Original Investigation

Effect of Dextromethorphan-Quinidine on Agitation in Patients With Alzheimer Disease Dementia
A Randomized Clinical Trial

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IMPORTANCE Agitation is common among patients with Alzheimer disease; safe, effective treatments are lacking.

OBJECTIVE To assess the efficacy, safety, and tolerability of dextromethorphan hydrobromide–quinidine sulfate for Alzheimer disease–related agitation.

DESIGN, SETTING, AND PARTICIPANTS Phase 2 randomized, multicenter, double-blind, placebo-controlled trial using a sequential parallel comparison design with 2 consecutive 5-week treatment stages conducted August 2012–August 2014. Patients with probable Alzheimer disease, clinically significant agitation (Clinical Global Impressions–Severity agitation score ≥4), and a Mini-Mental State Examination score of 8 to 28 participated at 42 US study sites. Stable dosages of antidepressants, antipsychotics, hypnotics, and antidementia medications were allowed.

INTERVENTIONS In stage 1, 220 patients were randomized in a 3:4 ratio to receive dextromethorphan-quinidine (n = 93) or placebo (n = 127). In stage 2, patients receiving dextromethorphan-quinidine continued; those receiving placebo were stratified by response and rerandomized in a 1:1 ratio to dextromethorphan-quinidine (n = 59) or placebo (n = 60).

MAIN OUTCOMES AND MEASURES The primary end point was change from baseline on the Neuropsychiatric Inventory (NPI) Agitation/Aggression domain (scale range, 0 [absence of symptoms] to 12 [symptoms occur daily and with marked severity]).

RESULTS A total of 194 patients (88.2%) completed the study. With the sequential parallel comparison design, 152 patients received dextromethorphan-quinidine and 127 received placebo during the study. Analysis combining stages 1 (all patients) and 2 (rerandomized placebo nonresponders) showed significantly reduced NPI Agitation/Aggression scores for dextromethorphan-quinidine vs placebo (ordinary least squares *z* statistic, −3.95; $P < .001$). In stage 1, mean NPI Agitation/Aggression scores were reduced from 7.1 to 3.8 with dextromethorphan-quinidine and from 7.0 to 5.3 with placebo. Between-group treatment differences were significant in stage 1 (least squares mean, −1.5; 95% CI, −2.3 to −0.7; $P<.001$). In stage 2, NPI Agitation/Aggression scores were reduced from 5.8 to 3.8 with dextromethorphan-quinidine and from 6.7 to 5.8 with placebo. Between-group treatment differences were also significant in stage 2 (least squares mean, −1.6; 95% CI, −2.9 to −0.3; $P=.02$). Adverse events included falls (8.6% for dextromethorphan-quinidine vs 3.9% for placebo), diarrhea (5.9% vs 3.1% respectively), and urinary tract infection (5.3% vs 3.9% respectively). Serious adverse events occurred in 7.9% with dextromethorphan-quinidine vs 4.7% with placebo. Dextromethorphan-quinidine was not associated with cognitive impairment, sedation, or clinically significant QTc prolongation.

CONCLUSIONS AND RELEVANCE In this preliminary 10-week phase 2 randomized clinical trial of patients with probable Alzheimer disease, combination dextromethorphan-quinidine demonstrated clinically relevant efficacy for agitation and was generally well tolerated.

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Agitation and aggression are highly prevalent in patients with dementia[1,2] and are associated with distress for patients and caregivers, greater risk of institutionalization, and accelerated progression to severe dementia and death.[3-5] Nonpharmacological interventions are recommended as first-line therapy, but many patients fail to respond, and pharmacotherapy is often needed.[5-7] Although many classes of psychotropic drugs are prescribed for agitation, safety concerns and modest or unproven efficacy limit their utility. Antipsychotics have shown benefit for Alzheimer disease–related psychosis, but their use is associated with excess mortality, cerebrovascular events, sedation, falls, cognitive impairment, metabolic syndrome, parkinsonism, and tardive dyskinesia.[5,8] A recent trial showed that citalopram, a selective serotonin reuptake inhibitor, was associated with improvement in agitation in Alzheimer disease but was associated with prolonged QTc interval and mild cognitive decline.[9] Safe and effective therapies targeting Alzheimer disease–related agitation are needed.[5]

CGIS *Clinical Global Impressions–Severity*

MMSE *Mini-Mental State Examination*

NPI *Neuropsychiatric Inventory*

QTcF *Fridericia-corrected QT interval*

The combination of dextromethorphan hydrobromide and quinidine sulfate is approved for the treatment of pseudobulbar affect in the United States and European Union. Dextromethorphan is a low-affinity, uncompetitive *N*-methyl-D-aspartate receptor antagonist,[10] σ_1 receptor agonist,[11] serotonin and norepinephrine reuptake inhibitor,[12] and neuronal nicotinic $\alpha_3\beta_4$ receptor antagonist.[13] Evidence suggesting a potential effect of dextromethorphan-quinidine for agitation comes from controlled clinical trial data in nondemented patients with pseudobulbar affect,[14] published case descriptions,[15] and anecdotal reports of improvement in patients with dementia, pseudobulbar affect, and symptoms suggestive of agitation.

Herein we report the results of a randomized clinical trial to assess the efficacy and safety of dextromethorphan-quinidine for moderate to severe agitation associated with Alzheimer disease.

Methods

Trial Design and Setting

This randomized, double-blind, placebo-controlled, 10-week trial was conducted at 42 US sites including outpatient Alzheimer disease clinics and assisted living and nursing facilities. This clinical trial was conducted using the Trimentum (Pharmaco Investments Inc) sequential parallel comparison design method, under license from PPD Development LP, consisting of 2 consecutive 5-week stages to enhance the ability to detect a treatment signal even in the context of a robust placebo response (eFigure in Supplement 1).[16] An independent data and safety monitoring board oversaw the study, and institutional review boards at each site approved the study protocol and its amendments (see Supplement 2 for trial protocol and Supplement 3 for statistical analysis plan). All patients or authorized representatives or caregivers provided written informed consent.

Participants

Eligible patients were aged 50 to 90 years with probable Alzheimer disease (based on 2011 National Institute on Aging–Alzheimer Association criteria) and clinically significant agitation, defined as a state of poorly organized and purposeless psychomotor activity characterized by at least 1 of the following: aggressive verbal (eg, screaming, cursing), aggressive physical (eg, destroying objects, grabbing, fighting), or nonaggressive physical (eg, pacing, restlessness) behaviors.[17] Eligible patients had behavioral symptoms that interfered with daily routine, were severe enough to warrant pharmacological treatment, scored 4 or higher (moderately ill) on the Clinical Global Impressions–Severity (CGIS) scale for agitation,[18] and had a Mini-Mental State Examination (MMSE) score of 8 to 28. Stable dosages of Alzheimer disease medications (≥2 months; memantine and/or acetylcholinesterase inhibitors) and specified antidepressants, antipsychotics, or hypnotics (≥1 month; including short-acting benzodiazepines and nonbenzodiazepines) were allowed; dosages were to remain stable throughout the study.

Exclusion criteria were non–Alzheimer disease dementia; agitation not secondary to Alzheimer disease; hospitalization in a mental health care facility; significant depression (Cornell Scale for Depression in Dementia score ≥10); schizophrenia or schizoaffective or bipolar disorder; myasthenia gravis (because quinidine use is contraindicated); clinically significant/unstable systemic disease; history of complete heart block, QTc prolongation, or torsades de pointes; family history of congenital QT prolongation; history of postural or unexplained syncope within the last year; or substance/alcohol abuse within 3 years. First-generation antipsychotics and tricyclic and monoamine oxidase inhibitor antidepressants were not allowed.

Race and ethnicity were self-reported or provided by a knowledgeable informant based on categories defined by the US Food and Drug Administration (FDA) Guidance for Industry for Collection of Race and Ethnicity Data in Clinical Trials.

Interventions

In stage 1, patients were randomized 3:4 to receive oral administration of dextromethorphan-quinidine or matching placebo. Dextromethorphan-quinidine was dosed as 20/10 mg once daily in the morning (with placebo in the evening) for week 1. Dextromethorphan-quinidine was increased to twice daily for weeks 2 and 3 and then increased to 30/10 mg twice daily for weeks 4 and 5. In stage 2, patients receiving dextromethorphan-quinidine continued to receive 30/10 mg twice daily. Patients who received placebo during stage 1 were stratified by treatment response and rerandomized in a 1:1 ratio to receive dextromethorphan-quinidine (dosage escalated as described above) or matching placebo. Patients were considered responders at the end of stage 1 if their CGIS score for agitation was 3 (mildly ill) or lower and their Neuropsychi-

atric Inventory (NPI) Agitation/Aggression domain score decreased by 25% or more from baseline.

Oral lorazepam (maximum dosage of 1.5 mg/d and maximum of 3 days in a 7-day period) was allowed as rescue medication for agitation if deemed necessary by the study investigator.

Outcomes

The prespecified primary efficacy end point was change from baseline in the NPI Agitation/Aggression domain. Each NPI domain was rated by the caregiver for symptom frequency (1-4: occasionally [less than once per week], often [about once per week], frequently [several times per week], or very frequently [once or more per day], respectively) and severity (1-3: mild, moderate, or marked, respectively); a score of 0 indicated no symptoms. The NPI's scoring yields a composite (frequency × severity) score of 1 to 12 for each positively endorsed domain.

Secondary efficacy end points included changes from baseline in NPI total score (range, 0-144), individual NPI domain scores, and NPI composite scores comprising the Agitation/Aggression, Aberrant Motor Behavior, and Irritability/Lability domains plus either the Anxiety domain (NPI4A) or the Disinhibition domain (NPI4D). An NPI Caregiver Distress score for each positively endorsed NPI domain captured how emotionally distressing the caregiver found the behavior (range, 0-5; not at all to very severely or extremely). Alzheimer Disease Cooperative Study (ADCS) Clinical Global Impression of Change scores (range, 1-7; marked improvement to marked worsening) and Patient Global Impression of Change scores, rated by a caregiver (range, 1-7; very much improved to very much worse), were assessed at weeks 5 and 10 and provided measures of clinical meaningfulness. Additional secondary end points included the ADCS Activities of Daily Living Inventory (range, 0-54; higher scores signifying better function); Cornell Scale for Depression in Dementia (range, 0-38; higher scores signifying more severe depression); Caregiver Strain Index (range, 0-13; higher scores signifying higher stress levels); Quality of Life–Alzheimer Disease score (range, 13-52; higher scores signifying better quality of life); and psychotropic medication changes/rescue use of lorazepam. Cognition was assessed using the MMSE (range, 0-30; lower scores signifying greater cognitive impairment) and the Alzheimer Disease Assessment Scale–Cognitive Subscale (range, 0-70; higher scores signifying greater cognitive impairment). Safety outcomes included adverse events, vital signs, clinical laboratory test results, and electrocardiographic findings. Results for QT interval were corrected for variation in heart rate and calculated according to the formula of Fridericia (QTcF): $(QT/\sqrt[3]{[RR]})$.[19]

Sample Size Calculation

In published treatment studies for dementia-related agitation, standard deviation estimates for change in NPI Agitation/Aggression scores range from 3.1 to 5.2 points.[20-22] Assuming an SD of 5.0 points and based on a 2-sided, 2-sample comparison of means from independent samples at the .05 significance level, a sample size of 196 patients would provide 90% power to detect a mean difference of 2.5 points. The sample size calculation was based on a parallel design because there was no precedent for a sequential parallel comparison design trial of agitation in Alzheimer disease.

Randomization

The randomization scheme was designed by the sponsor and managed by the contract research organization using an interactive Web response system. The randomization in stage 1 was stratified by baseline cognitive function (MMSE score of >15 vs ≤15) and agitation severity (CGIS score of 4-5 vs 6-7); blocked randomization ensured treatment balance in each stratum.

Masking

Dextromethorphan-quinidine and placebo capsules were identical in appearance. The sponsor, patients, caregivers, and investigators were unaware of treatment assignment. All study sites, patients, and caregivers were blinded to the use of sequential parallel comparison design and unaware of the responder criteria and midstudy rerandomization.

Statistical Analysis

The safety analysis set included all patients who took at least 1 dose of study medication. The modified intention-to-treat analysis set for efficacy included all patients with a postbaseline NPI Agitation/Aggression assessment in stage 1. In primary analysis, missing data were imputed using last observation carried forward; in sensitivity analysis, missing data were handled using a mixed-effects model assuming a missing-at-random mechanism.

Primary and secondary efficacy end points were analyzed based on published sequential parallel comparison design methods[16,23] analyzing data from both 5-week stages with 1:1 weighting using ordinary least squares and including all patients in stage 1 and only the rerandomized placebo nonresponders in stage 2. The primary study end-point analysis was prespecified; no correction was performed to address multiplicity in the secondary end points. Dextromethorphan-quinidine and placebo groups were compared using 2-sided tests at the $\alpha = .05$ level of significance. Additionally, analysis of covariance with treatment as the fixed effect and baseline as the covariate was used to compare treatment group means at each stage and visit, separately. To simulate a 10-week parallel-group design, we also conducted a prespecified comparison of NPI Agitation/Aggression scores between patients who were randomized to receive only dextromethorphan-quinidine vs only placebo for the entire 10 weeks of the trial (regardless of responder status). All statistical analyses were performed using SAS version 9.1 or higher (SAS Institute Inc).

Given the use of sequential parallel comparison design methods and to ensure findings from the primary analysis, additional exploratory sensitivity analyses of the primary end point were carried out. One used the repeated-measures model (prespecified) described by Doros et al[24] to test the potential statistical effect of missing data and the exclusion of rerandomized placebo "responders" in stage 2. This model uses all

available data from the NPI Agitation/Aggression domain. Three separate models were used to estimate treatment effect and included data collected at baseline, end of stage 1, and end of stage 2, with a general model that allows inclusion of data from intermediate visits. Based on an FDA recommendation, the second sensitivity analysis of the primary end point, using the seemingly unrelated regression method[24-26] in the sequential parallel comparison design instead of the ordinary least squares method, was conducted after unblinding of the study to address whether missing data could be missing not at random. In addition, a prespecified exploratory analysis of the primary end point was carried out that used the same sequential parallel comparison design method described above for the primary analysis but including both placebo responders and nonresponders who were rerandomized in stage 2.

Results

Patients

Patients were recruited between July 23, 2012, and May 22, 2014; the last patient completed the study on July 31, 2014, and the study closed August 30, 2014, at expiration of the 30-day safety reporting window. All 220 randomized patients (126 women and 94 men) were included in the safety analysis set; 218 patients comprised the modified intention-to-treat analysis set for efficacy, and 194 (88.2%) completed the study (**Figure 1**). With the sequential parallel comparison design and rerandomization of the placebo group on entry into stage 2, a total of 152 patients received dextromethorphan-quinidine (93 starting from stage 1 and an additional 59 rerandomized from the placebo group in stage 2) and 127 patients received placebo, resulting in an approximately 26.7% greater exposure to dextromethorphan-quinidine (1153 patient-weeks) than to placebo (911 patient-weeks). Seventeen patients (11.2%) discontinued the study while receiving dextromethorphan-quinidine and 9 (7.1%) while receiving placebo, including 8 (5.3%) and 4 (3.1%) for adverse events, respectively. Patient characteristics were well balanced across treatment groups (**Table 1**).

Efficacy Outcomes

Primary End Point

Dextromethorphan-quinidine significantly improved the NPI Agitation/Aggression score compared with placebo in the primary sequential parallel comparison design analysis (ordinary least squares z statistic, −3.95; $P < .001$). Results for each stage also favored dextromethorphan-quinidine over placebo (**Table 2**). In stage 1, mean NPI Agitation/Aggression scores were reduced from 7.1 (SD, 2.6) to 3.8 (SD, 3.3) with dextromethorphan-quinidine and from 7.0 (SD, 2.4) to 5.3 (SD, 3.2) with placebo, with a least squares mean treatment difference of −1.5 (95% CI, −2.3 to −0.7; $P < .001$). Differential response was noted by week 1 (least squares mean, −0.8; 95% CI, −1.5 to −0.03; $P = .04$) (**Figure 2**A). In stage 2 (placebo nonresponders rerandomized to either dextromethorphan-quinidine or placebo), mean NPI Agitation/Aggression scores were reduced from 5.8 (SD, 3.0) to 3.8 (SD, 3.1) with dextromethorphan-quinidine and from 6.7 (SD, 2.8) to 5.8 (SD, 3.8) with placebo, with a least squares mean treatment difference of −1.6 (95% CI, −2.9 to −0.3; $P = .02$) (Figure 2B). The prespecified comparison of NPI Agitation/Aggression scores between patients who were randomized to receive only dextromethorphan-quinidine (n = 93) vs only placebo (n = 66) for the entire 10 weeks of the trial (regardless of responder status, simulating a parallel-group design) also favored dextromethorphan-quinidine over placebo (least squares mean treatment difference, −1.8; 95% CI, −2.8 to −0.7; $P = .003$) (Table 2 and Figure 2C). Response to dextromethorphan-quinidine compared with placebo did not appear to differ by disease stage. The stratified randomization by baseline MMSE score (>15 vs ≤15) and baseline CGIS score (4 or 5 vs 6 or 7) resulted in balanced treatment groups for both agitation and cognitive function. Supplemental analyses conducted to assess the potential influence of these factors did not suggest a difference in response.

The repeated-measures model and seemingly unrelated regression sensitivity analyses of the primary end point corroborated the statistical significance observed in the primary efficacy analysis (eTable in Supplement 1). The additional prespecified analysis that included both placebo responders and nonresponders who were rerandomized in stage 2 did not alter the significance or magnitude of effect of the primary analysis.

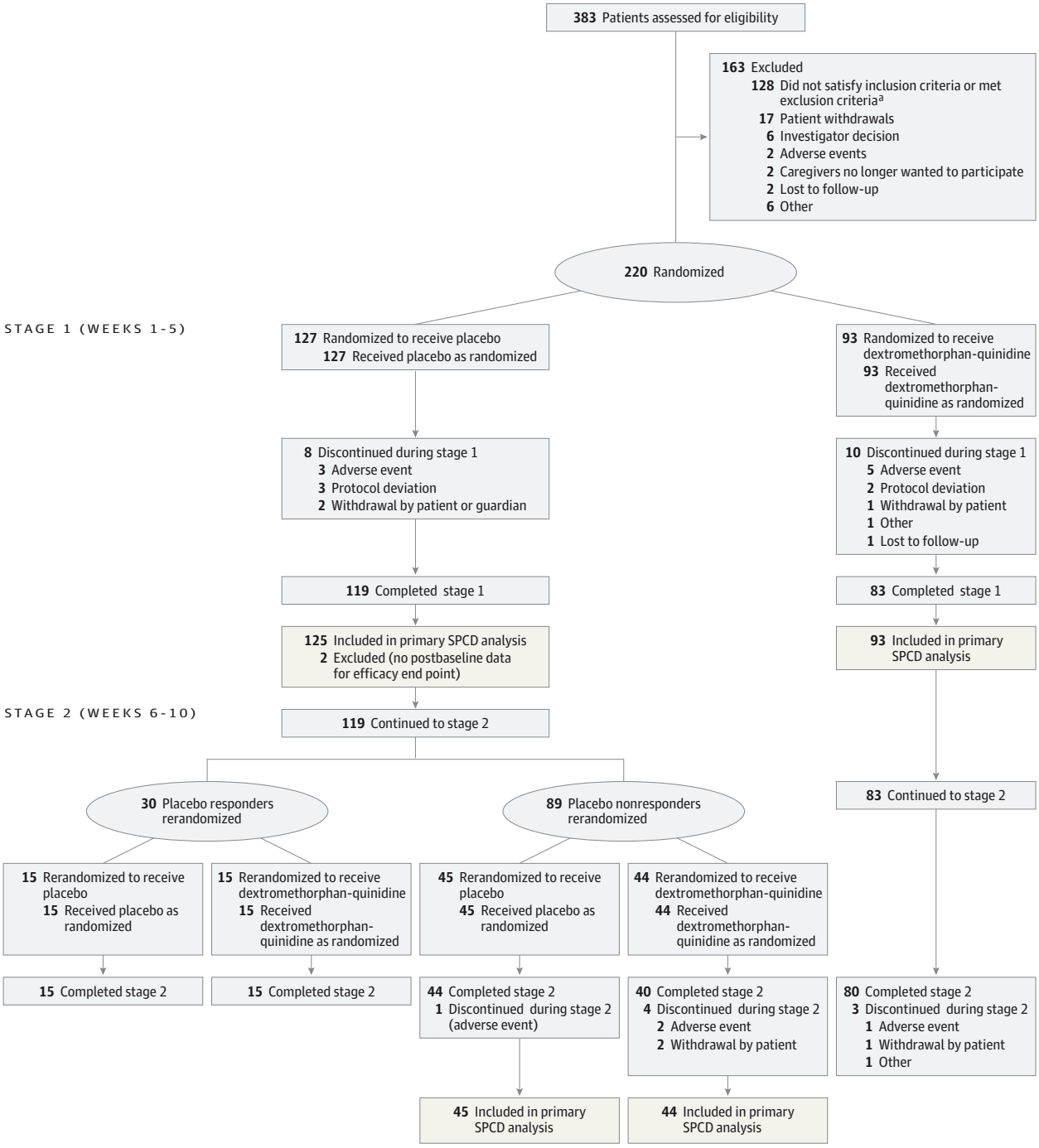
Secondary Outcomes

Sequential parallel comparison design analysis of prespecified secondary outcomes (Table 2 and **Table 3**) showed significant improvement favoring dextromethorphan-quinidine on global rating scores (Patient Global Impression of Change and ADCS Clinical Global Impression of Change), NPI total, NPI Aberrant Motor Behavior domain, NPI Irritability/Lability domain, NPI4A and NPI4D domain composites, NPI Caregiver Distress (as related to both the NPI Agitation/Aggression domain score and NPI total score), Caregiver Strain Index, and Cornell Scale for Depression in Dementia. Results for changes in the Quality of Life-Alzheimer Disease score, ADCS Activities of Daily Living Inventory, MMSE, and Alzheimer Disease Assessment Scale-Cognitive Subscale (an exploratory outcome) were not significant vs placebo. Post hoc analyses showed similar improvement in NPI Agitation/Aggression scores with dextromethorphan-quinidine in patients taking concomitant acetylcholinesterase inhibitors, memantine, antidepressants, or antipsychotics compared with those not receiving these agents. Lorazepam rescue medication was used by 10 of 152 patients (6.6%) during treament with dextromethorphan-quinidine and by 13 of 125 patients (10.4%) during treatment with placebo.

Safety and Tolerability

Treatment-emergent adverse events were attributed based on treatment assignment at the time of occurrence. Treatment-emergent adverse events were reported by 93 of 152 patients (61.2%) and 55 of 127 patients (43.3%) (safety set) during treatment with dextromethorphan-quinidine or

Figure 1. Participant Flow in a Trial of Dextromethorphan-Quinidine for Alzheimer Disease–Related Agitation



SPCD indicates sequential parallel comparison design. The modified intention-to-treat population included 218 patients (placebo, n = 125; dextromethorphan-quinidine, n = 93). At the end of stage 1, response for placebo group stratification was defined as having a Clinical Global Impressions–Severity (CGIS) score for agitation of 3 or lower (mildly ill) and a Neuropsychiatric Inventory Agitation/Aggression domain score decrease of 25% or more from baseline.

[a] Most common reasons for exclusions related to inclusion or exclusion criteria were not having a Mini-Mental State Examinination score between 8 and 28, inclusive (n=26); not having a CGIS score for agitation of at least 4 (n=25); having a personal history of complete heart block, QTc prolongation, or torsade de pointes (n=21); having coexistent clinically significant or unstable systematic disease (n=18); taking a disallowed medication (n=5); and taking an allowed medication but at an unstable dose or duration (n=5).

placebo, respectively. The most commonly occurring treatment-emergent adverse events (>3% and greater than placebo) were falls (8.6% vs 3.9%), diarrhea (5.9% vs 3.1%), urinary tract infection (5.3% vs 3.9%), and dizziness (4.6% vs 2.4%) for dextromethorphan-quinidine vs placebo, respectively. Serious adverse events occurred in 12 patients

Table 1. Baseline Demographic and Clinical Characteristics[a]

Characteristics	Dextromethorphan-Quinidine (n = 93)[b]	Placebo (n = 127)[b]
Age, mean (SD), y	77.8 (8.0)	77.8 (7.2)
Age ≥75 y	68 (73.1)	86 (67.7)
Women	52 (55.9)	74 (58.3)
Race		
White	84 (90.3)	118 (92.9)
Black or African American	5 (5.4)	6 (4.7)
Asian	3 (3.2)	1 (0.8)
Native Hawaiian or other Pacific Islander	1 (1.1)	0
Other	0	2 (1.6)
Ethnicity		
Hispanic or Latino	7 (7.5)	13 (10.2)
Residence		
Outpatient	82 (88.2)	111 (87.4)
Assisted living	5 (5.4)	10 (7.9)
Nursing home	6 (6.5)	6 (4.7)
Concomitant medications		
Acetylcholinesterase inhibitors	67 (72.0)	95 (74.8)
Memantine	43 (46.2)	66 (52.0)
Antidepressants	57 (61.3)	65 (51.2)
Antipsychotics	16 (17.2)	29 (22.8)
Benzodiazepines	6 (6.5)	12 (9.5)
Benzodiazepine-like derivatives	6 (6.5)	12 (9.5)
History of falls	16 (17.2)	16 (12.6)
Rating scale scores, mean (SD)[c]		
Clinical Global Impressions-Severity score for agitation	4.4 (0.6)	4.5 (0.7)
No. (%) with score		
4 (moderately ill)	61 (65.6)	77 (61.6)
5 (markedly ill)	28 (30.1)	38 (30.4)
6 or 7 (severely ill or among the most extremely ill patient)	4 (4.3)	10 (8.0)
Neuropsychiatric Inventory		
Agitation/Aggression domain	7.1 (2.6)	7.0 (2.4)
Total score	40.1 (19.6)	38.0 (18.7)
Aberrant Motor Behavior domain[d]	4.0 (0-8)	2.0 (0-6)
Irritability/Lability domain	5.8 (3.7)	5.4 (3.2)
NPI4A composite	20.9 (9.4)	20.1 (8.3)
NPI4D composite	19.8 (9.1)	18.5 (9.2)
Caregiver distress		
Agitation	3.3 (0.9)	3.0 (1.0)
Total score	17.9 (8.0)	17.0 (8.3)
Caregiver Strain Index	6.9 (3.2)	6.8 (3.6)
Cornell Scale for Depression in Dementia	5.9 (2.4)	5.8 (2.4)
Quality of Life-Alzheimer Disease scale		
Patient	36.5 (7.4)	37.2 (6.4)
Caregiver	30.9 (6.0)	30.1 (6.0)
Mini-Mental State Examination	17.4 (6.0)	17.2 (5.8)
Alzheimer Disease Assessment Scale-Cognitive Subscale	30.6 (14.1)	32.0 (15.2)
Alzheimer Disease Cooperative Study-Activities of Daily Living Inventory	35.8 (11.9)	34.1 (12.8)

Abbreviations: NPI4A, the sum of Neuropsychiatric Inventory Agitation/Aggression, Irritability/Lability, Aberrant Motor Behavior, and Anxiety domain scores; NPI4D, the sum of Neuropsychiatric Inventory Agitation/Aggression, Irritability/Lability, Aberrant Motor Behavior, and Disinhibition domain scores.

[a] Data are expressed as No. (%) of participants unless otherwise indicated.

[b] Safety analysis set at randomization.

[c] Modified intention-to-treat analysis set for efficacy analysis (dextromethorphan-quinidine, n = 93; placebo, n = 125) at stage 1 baseline.

[d] Presented as median (interquartile range). At baseline, the mean Neuropsychiatric Inventory Aberrant Motor Behavior domain scores were 4.3 (SD, 4.4) for dextromethorphan-quinidine and 3.5 (SD, 4.2) for placebo.

(7.9%) receiving dextromethorphan-quinidine and in 6 (4.7%) receiving placebo. Serious adverse events in patients receiving dextromethorphan-quinidine included chest pain (n = 2), anemia, acute myocardial infarction (occurring 2 days after dosing ended), bradycardia, kidney infection, femur fracture, dehydration, colon cancer, cerebrovascular

Table 2. Summary of Efficacy Outcome Measures in the Modified Intention-to-Treat Population

Outcome Measure and Study Stage[a]	No. of Participants		Change From Baseline, Mean (95% CI)		P Value by Stage[b]	Least Squares Mean Treatment Difference (95% CI)[c]	P Value by SPCD[b,d]
	Dextromethorphan-Quinidine	Placebo	Dextromethorphan-Quinidine	Placebo			
NPI Agitation/Aggression domain[e]							
Stage 1[a]	93	125	−3.3 (−3.9 to −2.6)	−1.7 (−2.3 to −1.2)	<.001	−1.5 (−2.3 to −0.7)	<.001
Stage 2[a]	44	45	−2.0 (−3.0 to −1.0)	−0.8 (−1.9 to 0.2)	.02	−1.6 (−2.9 to −0.3)	
10 wk[f]	93	66	−3.6 (−4.3 to −2.9)	−1.9 (−2.8 to −1.0)	.001	−1.8 (−2.8 to −0.7)	.003
NPI total score[e]							
Stage 1[a]	93	125	−13.5 (−17.1 to −9.9)	−8.5 (−11.0 to −5.9)	.03	−4.2 (−8.0 to −0.4)	.01
Stage 2[a]	44	45	−6.0 (−9.7 to −2.2)	−2.5 (−6.0 to 1.1)	.15	−3.8 (−9.0 to 1.4)	
10 wk[f]	93	66	−16.0 (−19.5 to −12.5)	−10.1 (−14.7 to −5.5)	.02	−5.7 (−10.7 to −0.7)	NA
NPI Aberrant Motor Behavior domain[e]							
Stage 1[a]	93	125	−1.2 (−2.0 to −0.4)	−0.4 (−1.1 to 0.3)	.39	−0.4 (−1.3 to 0.5)	.03
Stage 2[a]	44	45	−0.8 (−1.6 to −0.1)	0.4 (−0.6 to 1.3)	.04	−1.2 (−2.4 to −0.1)	
10 wk[f]	93	66	−1.3 (−2.1 to −0.5)	0.1 (−0.7 to 0.8)	.03	−1.0 (−1.9 to −0.1)	NA
NPI Irritability/Lability domain[e]							
Stage 1[a]	93	125	−2.2 (−3.0 to −1.4)	−1.2 (−1.8 to −0.6)	.09	−0.7 (−1.5 to 0.1)	.03
Stage 2[a]	44	45	−1.0 (−2.0 to 0.04)	−0.7 (−1.8 to 0.5)	.14	−0.9 (−2.2 to 0.3)	
10 wk[f]	93	66	−2.4 (−3.3 to −1.6)	−1.8 (−2.8 to −0.7)	.38	−0.4 (−1.4 to 0.6)	NA
NPI4A composite[e]							
Stage 1[a]	93	125	−7.3 (−9.1 to −5.4)	−4.5 (−6.0 to −3.0)	.03	−2.4 (−4.6 to −0.2)	.001
Stage 2[a]	44	45	−4.8 (−6.9 to −2.7)	−1.4 (−3.8 to 1.0)	.01	−3.9 (−7.0 to −0.9)	
10 wk[f]	93	66	−8.5 (−10.4 to −6.7)	−5.0 (−7.4 to −2.5)	.01	−3.4 (−6.1 to −0.7)	NA
NPI4D composite[e]							
Stage 1[a]	93	125	−7.6 (−9.4 to −5.7)	−4.0 (−5.5 to −2.6)	.006	−3.0 (−5.1 to −0.9)	<.001
Stage 2[a]	44	45	−4.6 (−6.8 to −2.4)	−1.9 (−4.2 to 0.4)	.02	−3.5 (−6.5 to −0.5)	
10 wk[f]	93	66	−8.3 (−10.1 to −6.5)	−5.0 (−7.4 to −2.6)	.02	−3.0 (−5.5 to −0.4)	NA
NPI Caregiver Distress agitation score[e]							
Stage 1[a]	93	125	−1.4 (−1.6 to −1.0)	−0.6 (−0.8 to −0.4)	<.001	−0.7 (−1.0 to −0.3)	.01
Stage 2[a]	44	45	−0.5 (−0.9 to −0.004)	−0.7 (−1.2 to −0.2)	.49	−0.2 (−0.8 to 0.4)	
10 wk[f]	93	66	NA	NA	NA	NA	NA
NPI Caregiver Distress total score[e]							
Stage 1[a]	93	125	−6.6 (−8.2 to −5.0)	−3.6 (−4.8 to −2.5)	NA	NA	.01
Stage 2[a]	44	45	−2.6 (−4.3 to −1.0)	−2.0 (−3.8 to −0.3)	NA	NA	
10 wk[f]	93	66	NA	NA	NA	NA	NA
Caregiver Strain Index[e]							
Stage 1[a]	93	125	−1.2 (−1.7 to −0.7)	−0.6 (−0.9 to −0.2)	.03	−0.6 (−1.2 to −0.1)	.05
Stage 2[a]	44	45	−0.2 (−0.7 to 0.3)	0.1 (−0.5 to 0.6)	.42	−0.3 (−1.0 to 0.4)	
10 wk[f]	93	66	−1.2 (−1.7 to 0.6)	−0.4 (−0.9 to 1.3)	.04	−0.8 (−1.6 to −0.02)	NA
Cornell Scale for Depression in Dementia[g]							
Stage 1[a]	88	123	−1.0 (−1.8 to −0.3)	0.6 (−0.1 to 1.3)	.002	−1.6 (−2.5 to −0.6)	.02
Stage 2[a]	43	44	−0.9 (−1.8 to −0.004)	−0.7 (−1.5 to 0.1)	.75	−0.2 (−1.3 to 0.9)	
10 wk[f]	88	64	−1.2 (−2.0 to −0.4)	0.4 (−0.6 to 1.5)	.03	−1.3 (−2.6 to −0.1)	NA
ADCS Clinical Global Impression of Change score for agitation[h]							
Stage 1[a]	88	123	3.0 (2.8 to 3.3)	3.6 (3.4 to 3.8)	<.001	−0.6 (−0.9 to −0.3)	<.001
Stage 2[a]	42	42	3.3 (2.9 to 3.6)	3.7 (3.3 to 4.2)	.07	−0.5 (−1.0 to 0.1)	
10 wk[f]	82	59	2.7 (2.3 to 3.1)	3.3 (3.0 to 3.7)	.02	−0.5 (−0.9 to −0.1)	NA

(continued)

Table 2. Summary of Efficacy Outcome Measures in the Modified Intention-to-Treat Population (continued)

Outcome Measure and Study Stage[a]	No. of Participants		Change From Baseline, Mean (95% CI)		*P* Value by Stage[b]	Least Squares Mean Treatment Difference (95% CI)[c]	*P* Value by SPCD[b,d]
	Dextromethorphan-Quinidine	Placebo	Dextromethorphan-Quinidine	Placebo			
Patient Global Impression of Change[i]							
Stage 1[a]	88	123	3.1 (2.8 to 3.3)	3.6 (3.4 to 3.8)	.001	−0.6 (−0.9 to −0.2)	.001
Stage 2[a]	43	44	3.2 (2.8 to 3.6)	3.8 (3.3 to 4.2)	.04	−0.6 (−1.1 to −0.1)	
10 wk[f]	81	59	2.9 (2.7 to 3.2)	3.5 (3.2 to 3.8)	.007	−0.6 (−1.0 to −0.2)	NA
Quality of Life–Alzheimer Disease scale							
Patient[h]							
Stage 1[a]	87	116	1.3 (−0.03 to 2.6)	0.0 (−1.0 to 0.9)	.14	1.1 (−0.4 to 2.6)	.16
Stage 2[a]	40	40	1.5 (−0.1 to 3.1)	0.7 (−0.7 to 2.0)	.50	0.7 (−1.4 to 2.7)	
10 wk[f]	87	61	0.7 (−0.7 to 2.1)	0.5 (−1.1 to 2.0)	.96	−0.1 (−2.0 to 1.9)	NA
Caregiver[h,j]							
Stage 1[a]	88	123	0.4 (−0.5 to 1.3)	0.3 (−0.5 to 1.1)	.63	0.3 (−0.9 to 1.5)	.47
Stage 2[a]	43	43	−0.3 (−1.5 to 0.9)	0.9 (−0.4 to 2.2)	.24	1.1 (−2.8 to 0.7)	
10 wk[f]	88	64	1.3 (0.2 to 2.4)	0.9 (−0.5 to 2.4)	.28	0.9 (−0.7 to 2.6)	NA
ADCS Activities of Daily Living Inventory[h]							
Stage 1[a]	88	123	−0.9 (−1.8 to −0.04)	−0.8 (−1.5 to −0.1)	.90	−0.1 (−1.2 to 1.1)	.16
Stage 2[a]	43	44	−2.0 (−3.4 to −0.5)	−0.6 (−1.7 to 0.4)	.12	−1.4 (−3.1 to 0.4)	
10 wk[f]	88	64	−0.8 (−1.8 to 0.2)	−1.8 (−2.9 to 0.7)	.17	1.0 (−0.5 to 2.5)	NA
Mini-Mental State Examination total score[g]							
Stage 1[a]	88	122	0.2 (−0.4 to 0.9)	−0.3 (−0.8 to 0.2)	.20	0.5 (−0.3 to 1.3)	.05
Stage 2[a]	42	44	0.3 (−0.5 to 1.2)	−0.5 (−1.3 to 0.2)	.15	0.8 (−0.3 to 2.0)	
10 wk[f]	88	63	0.1 (−0.5 to 0.8)	−0.6 (−1.5 to 0.3)	.21	0.7 (−0.4 to 1.8)	NA
Alzheimer Disease Assessment Scale–Cognitive Subscale[h]							
Stage 1[a]	87	121	−0.9 (−2.5 to 0.6)	0.3 (−5.7 to 1.3)	.11	−1.4 (−3.0 to 0.3)	.20
Stage 2[a]	42	43	0.3 (−1.4 to 1.9)	0.8 (−0.7 to 2.3)	.64	−0.5 (−2.8 to 1.7)	
10 wk[f]	81	58	−0.7 (−1.9 to 0.7)	1.2 (−0.2 to 2.4)	.07	−1.7 (−3.5 to 0.2)	NA

Abbreviations: ADCS, Alzheimer Disease Cooperative Study; NA, not assessed; NPI, Neuropsychiatric Inventory; NPI4A, the sum of Neuropsychiatric Inventory Agitation/Aggression, Irritability/Lability, Aberrant Motor Behavior, and Anxiety domain scores; NPI4D, the sum of Neuropsychiatric Inventory Agitation/Aggression, Irritability/Lability, Aberrant Motor Behavior, and Disinhibition domain scores.

[a] Stage 1 includes all patients and measures change from stage 1 baseline to week 5 for each outcome. Stage 2 includes only rerandomized placebo nonresponders from stage 1 and measures change from stage 2 baseline (week 5) to week 10 for all outcomes except the Patient Global Impression of Change, which measures change from original stage 1 baseline to week 10.

[b] *P* value by stage for dextromethorphan-quinidine vs placebo is based on analysis of covariance with treatment as fixed effect and baseline as covariate; *P* value for SPCD analysis is based on ordinary least squares.

[c] Treatment difference = dextromethorphan-quinidine − placebo.

[d] Sequential parallel comparison design (SPCD) analysis was protocol specified for the primary efficacy analysis and combines results from all patients in stage 1 and from placebo nonresponders rerandomized in stage 2 based on a 50/50 weighting of the NPI Agitation/Aggression domain for each stage of the study.

[e] Assessed at baseline and weeks 1, 3, 5, 6, 8, and 10.

[f] The 10-week analysis includes only patients who continued their original treatment for their entire study participation (ie, took only dextromethorphan-quinidine or only placebo, thereby simulating a parallel-group design) and measures change from stage 1 baseline to week 10.

[g] Assessed at screening and weeks 5 and 10.

[h] Assessed at baseline and weeks 5 and 10.

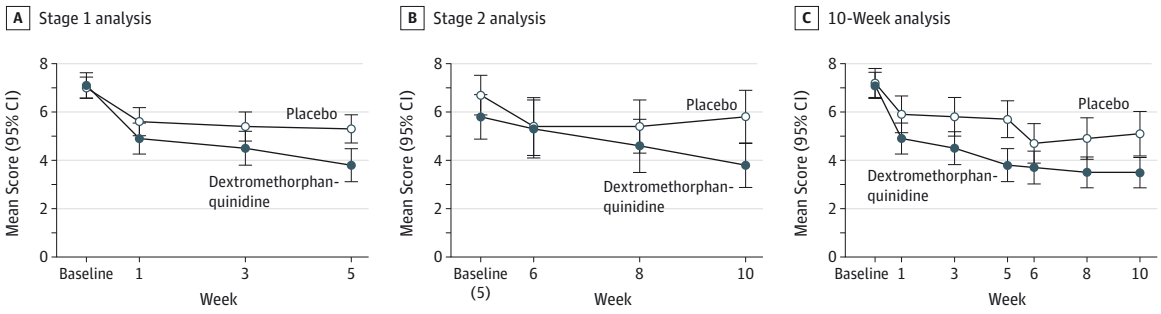
[i] Assessed at weeks 5 and 10.

[j] For the Quality of Life–Alzheimer Disease scale's caregiver response, the caregiver rates the patient's quality of life.

accident, aggression, and hematuria (n = 1 each). Serious adverse events in patients receiving placebo included idiopathic thrombocytopenic purpura, vertigo, pneumonia, gastroenteritis, contusion, transient ischemic attack, and agitation (n = 1 each). Eight patients (5.3%) receiving dextromethorphan-quinidine and 4 (3.1%) receiving placebo discontinued treatment owing to adverse events, including 4 (2.6%) and 2 (1.6%), respectively, for serious adverse events. No deaths occurred during the study.

Of the 13 patients who fell while receiving dextromethorphan-quinidine, 9 had a history of falls. Three fell 2 to 4 days after study completion, and 1 patient fell twice within 24 hours of

Figure 2. Mean Neuropsychiatric Inventory Agitation/Aggression Domain Scores by Stage and Visit for Patients Included in the Sequential Parallel Comparison Design and 10-Week Analyses



No. of participants[a]														
Dextromethorphan-quinidine	93	93	90	83	44	44	44	44	93	93	90	90	83	82	83
Placebo	125	124	121	119	45	45	45	45	66	65	65	65	60	60	60

A, Stage 1 (weeks 1-5); B, stage 2 (weeks 6-10) for placebo nonresponders rerandomized after stage 1; C, 10-week results (the 10-week secondary analysis includes only patients who continued the same treatment assignment throughout study participation; ie, were randomized to receive only dextromethorphan-quinidine or only placebo [excludes patients who were rerandomized from placebo to dextromethorphan-quinidine in stage 2], thus simulating a parallel-group design). Analysis-of-covariance models with treatment as fixed effect and baseline as covariate were used to compare mean change from baseline between groups at each time point. Baseline for stage 2 is the patients' scores at the start of stage 2. Least squares mean treatment differences are as follows: for stage 1, week 1, −0.8 (95% CI, −1.5 to −0.03; $P = .04$), week 3, −1.0 (95% CI, −1.8 to −0.2; $P = .01$), and week 5, −1.5 (95% CI, −2.3 to −0.7; $P < .001$); for stage 2, week 6, 0.7 (95% CI, −0.4 to 1.9; $P = .19$), week 8, −0.1 (95% CI, −1.3 to 1.2; $P = .93$), and week 10, −1.6 (95% CI, −2.9 to −0.3; $P = .02$); for 10-week analysis, week 1, −0.9 (95% CI, −1.8 to −0.04; $P = .047$), week 3, −1.3 (95% CI, −2.2 to −0.3; $P = .01$), week 5, −1.8 (95% CI, −2.7 to −0.9; $P < .001$), week 6, −0.9 (95% CI, −2.0 to 0.1; $P = .06$), week 8, −1.3 (95% CI, −2.4 to −0.3; $P = .01$), and week 10, −1.8 (95% CI, −2.8 to −0.7; $P = .003$).

[a] Observed cases.

receiving lorazepam rescue in both instances; no patient who fell while receiving placebo had a history of falls. Two falls were associated with serious adverse events; femur fracture in the dextromethorphan-quinidine group and contusion in the placebo group.

No clinically meaningful between-group differences in electrocardiographic findings were observed. The mean change in QTcF was 5.3 (SD, 14.06) milliseconds among patients receiving dextromethorphan-quinidine (n = 138) and −0.3 (SD, 12.96) milliseconds among patients receiving placebo (n = 60) at the final visit. Fifteen patients (10.3%) receiving dextromethorphan-quinidine (n=145) and 8 (6.7%) receiving placebo (n=120) had a QTcF increase of at least 30 milliseconds at any visit; 1 patient receiving placebo had a QTcF increase of greater than 60 milliseconds. No patient had a QTcF greater than 500 milliseconds.

Discussion

In this placebo-controlled randomized trial of dextromethorphan-quinidine for agitation in Alzheimer disease, we enrolled patients with moderate to severe symptoms who required pharmacological intervention. The Alzheimer disease–related agitation characteristics of patients in this study were generally consistent with the recently proposed definition of agitation from the International Psychogeriatric Association (IPA),[27] although patient emotional distress was not directly measured. As in the current study, the IPA definition requires the presence of behaviors causing excess disability that are not due to another medical, psychiatric, or substance-related disorder. Agitated behaviors may include excessive motor activity, verbal aggression, or physical aggression.[27] Baseline agitation severity and NPI Agitation/Aggression scores were also generally consistent with those of participants in the Citalopram for Agitation in Alzheimer Disease study.[9] Treatment with dextromethorphan-quinidine in this study demonstrated statistically significant efficacy on the primary end point and the majority of secondary end points across multiple measures rated by both clinicians and caregivers.

Improvement in the NPI Agitation/Aggression domain was statistically significant at week 1 and at every time point until study end, with exception of weeks 6 and 8 (during stage 2). The effects were considered to be clinically meaningful as reflected by improvement in ADCS Clinical Global Impression of Change and Patient Global Impression of Change scores, as well as on the measures of Caregiver Strain Index and NPI Caregiver Distress score. At the end of the 10-week treatment, 45.1% of participants treated only with dextromethorphan-quinidine (n = 82) were judged to have a "moderate" or "marked" improvement on ADCS Clinical Global Impression of Change vs 27.1% of participants who took only placebo (n = 59; $P = .008$). Similar results were also observed for Patient Global Impression of Change. Percentage improvement on the NPI Agitation/Aggression scores from baseline and proportion of patients achieving standard thresholds of response (eg, 30% or 50% response) were also used to gauge relevance of clinical response. The NPI manual (http://npitest.net/faqs.html), for instance, suggests that a 30% decrease in scores is generally clinically meaningful.

In this study, patients treated with only dextromethorphan-quinidine had a mean 50.7% reduction in the NPI Agitation/

Table 3. Summary of Categorical Efficacy Outcome in the Modified Intention-to-Treat Population

Study Stage	Categorical Response	No. (%) of Participants	
		Dextromethorphan-Quinidine	Placebo
Clinical Global Impressions-Severity Score for Agitation			
Baseline	Moderately ill	61 (65.6)	77 (61.6)
	Markedly ill	28 (30.1)	38 (30.4)
	Severely ill	4 (4.3)	9 (7.2)
	Among the most extremely ill	0	1 (0.8)
Alzheimer Disease Cooperative Study-Clinical Global Impression of Change Score for Agitation			
Stage 1[a]	Marked improvement	8 (9.1)	1 (0.8)
	Moderate improvement	22 (25.0)	13 (10.6)
	Minimal improvement	28 (31.8)	43 (35.0)
	No change	22 (25.0)	48 (39.0)
	Minimal worsening	7 (8.0)	12 (9.8)
	Moderate worsening	1 (1.1)	6 (4.9)
	Marked worsening	0	0
Stage 2[b]	Marked improvement	0	4 (9.5)
	Moderate improvement	11 (26.2)	2 (4.8)
	Minimal improvement	15 (35.7)	8 (19.0)
	No change	11 (26.2)	19 (45.2)
	Minimal worsening	4 (9.5)	6 (14.3)
	Moderate worsening	1 (2.4)	2 (4.8)
	Marked worsening	0	1 (2.4)
10 wk[c]	Marked improvement	9 (11.0)	6 (10.2)
	Moderate improvement	28 (34.1)	10 (16.9)
	Minimal improvement	27 (32.9)	18 (30.5)
	No change	14 (17.1)	15 (25.4)
	Minimal worsening	2 (2.4)	9 (15.3)
	Moderate worsening	1 (1.2)	0
	Marked worsening	1 (1.2)	1 (1.7)
Patient Global Impression of Change Score			
Stage 1[a]	Very much improved	10 (11.4)	2 (1.6)
	Much improved	24 (27.3)	23 (18.7)
	Minimally improved	20 (22.7)	30 (24.4)
	No change	20 (22.7)	40 (32.5)
	Minimally worse	13 (14.8)	23 (18.7)
	Much worse	1 (1.1)	4 (3.3)
	Very much worse	0	1 (0.8)
Stage 2[b]	Very much improved	3 (7.0)	3 (6.8)
	Much improved	10 (23.3)	4 (9.1)
	Minimally improved	14 (32.6)	11 (25.0)
	No change	10 (23.3)	13 (29.5)
	Minimally worse	4 (9.3)	9 (20.5)
	Much worse	2 (4.7)	4 (9.1)
	Very much worse	0	0
10 wk[c]	Very much improved	9 (11.1)	5 (8.5)
	Much improved	26 (32.1)	9 (15.3)
	Minimally improved	25 (30.9)	17 (28.8)
	No change	13 (16.0)	14 (23.7)
	Minimally worse	5 (6.2)	10 (16.9)
	Much worse	3 (3.7)	4 (6.8)
	Very much worse	0	0

[a] Stage 1 includes all patients and measures change from stage 1 baseline to week 5 for each outcome.

[b] Stage 2 includes only rerandomized placebo nonresponders from stage 1 and measures change from stage 2 baseline (week 5) to week 10 for all outcomes except the Patient Global Impression of Change, which measures change from original stage 1 baseline to week 10.

[c] The 10-week analysis includes only patients who continued their original assigned treatment for their entire study participation (ie, took only dextromethorphan-quinidine or only placebo, thereby simulating a parallel-group design) and measures change from stage 1 baseline to week 10.

Aggression scores from baseline to week 10 compared with 26.4% treated with only placebo (P = .001); this placebo response would not be deemed clinically meaningful. With respect to standard response thresholds, in the 10-week analysis, 55.9% of patients treated with only dextromethorphan-quinidine experienced at least a 50% reduction in the NPI

Agitation/Aggression score from baseline compared with 37.9% of patients receiving only placebo (P = .03). Furthermore, 65.6% of patients treated with only dextromethorphan-quinidine had at least a 30% reduction in NPI Agitation/Aggression scores from baseline compared with 47% of patients receiving only placebo (P = .02). Rates of response at the end of stage 1 (week 5) were comparable with those reported for the 10-week analysis in magnitude and significance compared with placebo. Combined, these between-group comparisons of response suggest that treatment with dextromethorphan-quinidine was consistently associated with a meaningful improvement in agitation, and with a magnitude that compares favorably with that found in prior studies included in a review published by Soto et al.[28] Significant improvements were also seen in the NPI4A and NPI4D composite scores comprising symptoms commonly observed in patients with Alzheimer disease–related agitation (Table 2).[29]

Dextromethorphan-quinidine was generally well tolerated in this elderly population receiving multiple concomitant medications and was not associated with cognitive impairment. Few patients discontinued because of adverse events, and most adverse events, including low rates of dizziness and diarrhea, were consistent with those observed in dextromethorphan-quinidine trials for pseudobulbar affect.[14,30,31] Falls were more common among patients receiving dextromethorphan-quinidine; an imbalance in prerandomization risk of falls and approximately 25% greater patient-days of exposure to dextromethorphan-quinidine may have contributed to the higher rates compared with placebo.

Dextromethorphan, the neurologically active component of the dextromethorphan-quinidine combination, has activity at receptors involved in modulating glutamate, serotonin, norepinephrine, and potentially other neurotransmitters, although the exact mechanism of action responsible for the reduction of dementia-associated agitation is not known. In earlier clinical studies, agitation in the context of dementia has been improved with drugs acting on serotonin (citalopram)[9] or glutamate (memantine) receptors,[32] lending support to the hypothesis that dextromethorphan exerts therapeutic effects on dementia-associated agitation through these and perhaps other central nervous system receptors.

To our knowledge, this is the first dementia-related trial to use a sequential parallel comparison design, an enrichment design chosen to address the potential of high placebo-associated improvement, as observed in previous trials evaluating neuropsychiatric symptoms in Alzheimer disease.[33,34] In studies using this design, the first stage randomizes more patients to placebo than to active treatment. In the second stage, placebo nonresponders from stage 1 are rerandomized and are included in the primary analysis. Pooled analysis of both stages maximizes the power to detect treatment differences and reduces the required sample size.[16] Consistent with prior studies using this design, while the placebo response in stage 2 (−0.8) among placebo nonresponders was smaller than in stage 1 (−1.7) and the response to active drug was also smaller in stage 2, the difference between active drug and placebo was still significant and had a standardized effect size of −0.34 (the standardized effect size in stage 1 was −0.505). Treatment effect was evident in both stages (even when placebo responders were included in the stage 2 comparison, a prespecified exploratory analysis). Improvement in NPI Agitation/Aggression was observed at week 1 (stage 1 and 10-week analyses) with the lower dextromethorphan-quinidine dose (20/10 mg) and appeared to increase over time. An analysis comparing patients who remained in their original randomized treatment group for the full 10-week study, which was prespecified to simulate a conventional 10-week parallel design, also showed a clinically and statistically significant effect on the primary end point and most secondary outcome measures favoring dextromethorphan-quinidine over placebo, consistent with sequential parallel comparison design analysis findings. Although stratification by disease stage measures such as cognitive function and severity of agitation did not appear to affect response to dextromethorphan-quinidine, the number of patients included in some strata used for these analyses were small, requiring confirmation of this observation in larger trials.

Strengths of the study include (1) use of the sequential parallel comparison design, with the intention of increasing study power by minimizing the effect of placebo response; (2) allowance of stable concomitant medications (including psychotropics), which closely reflects everyday clinical practice and adds to generalizability; (3) a high retention rate (88.2% across 10 weeks); (4) blinding of study sites to all aspects of the sequential parallel comparison design; (5) corroboration of efficacy observed for the primary efficacy end point by prespecified sensitivity analyses; and (6) consistent results among multiple significant secondary outcomes and the primary efficacy end point.

Limitations of this trial include a duration limited to 10 weeks and a dose-escalation schedule that limited evaluation of dose-response relationships. Aspects of the trial design, such as the exclusion of concomitant drugs related to quinidine, tricyclic antidepressants, monoamine oxidase inhibitors, or phenothiazines, as well as specific electrocardiographic/cardiac parameters that restricted patient enrollment, may limit the generalizability of study findings. Treatment at experienced trial sites by specialized clinicians under a clinical protocol prescribing frequent assessments may not reflect general practice. In addition, the patient sample consisted predominantly of outpatients; agitation in residents of nursing homes was underrepresented (5.5% of study participants). The treatment response may not be readily generalizable to patients in nursing homes and should be further explored.

Conclusions

In this 10-week phase 2 randomized clinical trial of patients with probable Alzheimer disease, the combination of dextromethorphan-quinidine demonstrated clinically relevant efficacy for agitation and was generally well tolerated. These preliminary findings require confirmation in additional clinical trials with longer treatment duration.

ARTICLE INFORMATION

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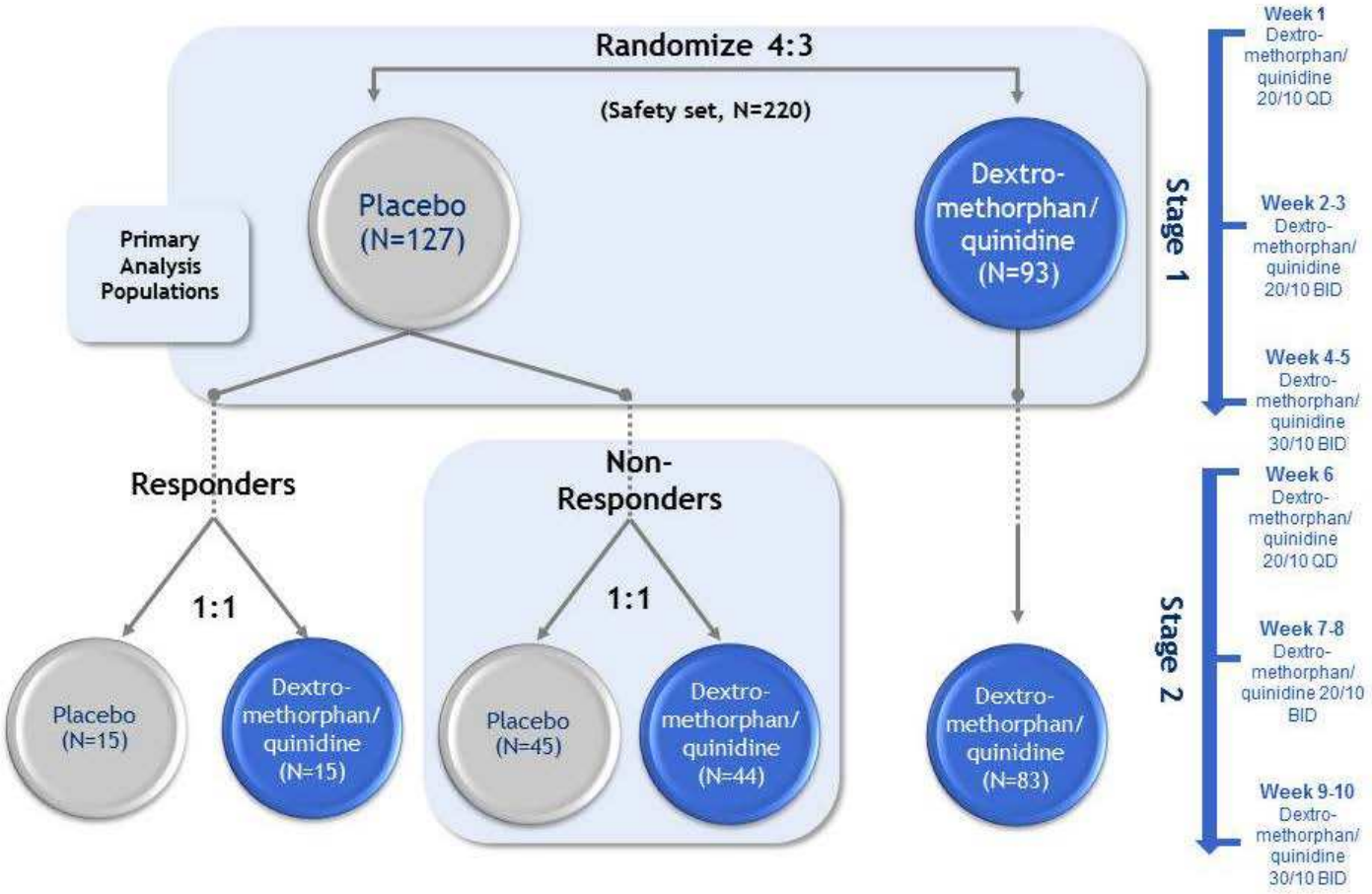
Supplementary Online Content

Cummings JL, Lyketsos CG, Peskind ER, et al. Effect of dextromethorphan-quinidine on agitation in patients with alzheimer disease dementia: a randomized clinical trial. doi:10.1001/jama.2015.10214

This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure. Study Design



Shading shows the patient groups included in the primary SPCD analysis (all patients randomized in Stage 1 (mITT population) and placebo nonresponders from Stage 1 that were rerandomized in Stage 2, mITT population stage 2). A “response” in Stage 1 was defined as a CGIS score of 1-3 (inclusive) at Visit 4 (week 5/end of Stage 1) and an NPI Agitation/Aggression domain score decrease of ≥ 25%; patients not meeting these criteria were considered “nonresponders”. BID = twice per day; QD = once daily.

eTable. Results of Repeated Measures Mixed Model (MMRM) and Seemingly Unrelated Regression (SUR) Sensitivity Analyses of the Primary Endpoint, Modified Intention-to-Treat Population

	Stage	N Dextromethorphan/ quinidine	N Placebo	Dextromethorphan/ quinidine, Mean (SD) Change from Baseline	Placebo, Mean (SD) Change from Baseline	Estimated Treatment Effect (95% CI)	Test Statistic[b]	*P* Value
MMRM Analysis								
NPI–Agitation/ Aggression[a]	1	93	125			-0.74 (-1.17, -0.31)	-3.30	.001
	Wk 1			-2.2 (2.9)	-1.4 (2.7)			
	Wk 3			-2.7 (3.2)	-1.6 (2.9)			
	Wk 5			-3.3 (3.0)	-1.7 (3.1)			
	2	142	60					
	Wk 6			-0.2 (2.8)	-0.9 (2.8)			
	Wk 8			-0.6 (3.1)	-0.7 (2.9)			
	Wk 10			-0.9 (3.4)	-0.5 (3.4)			
SUR Analysis								
NPI–Agitation/ Aggression[a]	1	93	125	-3.3 (3.0)	-1.7 (3.1)		15.5	<0.0001
	2	44	45	-2.0 (3.2)	-0.8 (3.6)			

[a]Assessed at baseline, weeks 1, 3, 5, 6, 8, and 10.

PROTOCOL TITLE:

A Phase 2, randomized, double-dummy, double-blind, placebo-controlled, 2-stage, sequential parallel study to assess the efficacy, safety, and tolerability of AVP-923 (dextromethorphan/quinidine) for the treatment of symptoms of agitation in patients with Alzheimer's disease.

Protocol:	12-AVR-131 – Amendment 3	**IND:** 114,374
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Protocol Amendment 3 (Version 4.0)

Summary of Changes

Section Number	Section Title	Description
Title Page	Title Page	The date, version number, and amendment number were changed to reflect date of finalization, version 4, amendment 3.
6.2.9	ADCS-CGIC	Clarified and revised the ADCS-CGIC assessments. At Day 36 (Visit 4), the ADCS-CGIC will be completed to assess change from the Baseline (Day 1) visit. At Day 70 (Visit 7), the ADCS-CGIC will be completed to assess change from Day 36 (Visit 4) and change from the Baseline (Day 1) visit. The ADCS-CGIC from Day 36 (Visit 4) to Day 70 (Visit 7) will be performed retrospectively for all patients who completed Visit 7 prior to Amendment 3 based on the existing ADCS-CGIC evaluation worksheets that allow the clinician to record assessments of clinical severity and of change over time.
Table 2	Study Schedule	Moved the urine pregnancy test from pre-dose to post-dose so all safety labs are collected after dosing.
6.4.1.5	Visit 4 (Day 36)	Clarified that the ADCS-CGIC assessments at Visit 4 (Day 36) is to assess change from Baseline. Moved the urine collection from pre-dose to post-dose so all safety labs are collected after dosing.
6.4.1.8	Visit 7 (Day 70)/ Early Termination	Clarified that the ADCS-CGIC assessments at Visit 7 (Day 70) is to assess change from Visit 4 and change from Baseline. Clarified timing for early termination visit. The visit should occur within 48 hours of the last dose of study medication and there is no specific time frame for the 12-lead ECG, safety labs, and PK samples for early termination patients.
Appendices	Appendices	Updated Appendix 10 to add assessment of change in ADCS-CGIC from Visit 7 to Visit 4.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AD	Alzheimer's Disease
ADAS-cog	Alzheimer's Disease Assessment Scale - cognitive subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory
ALS	Amyotrophic lateral sclerosis
ALT/SGPT	Alanine aminotransferase/serum glutamic-pyruvic transaminase
AMPA	Alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid
AST/SGOT	Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase
AUC	Area under the concentration-by-time curve
beta-hCG	Beta subunit of human chorionic gonadotropin
BP	Blood pressure
BUN	Blood urea nitrogen
CCSMHA	Cache County Study on Memory in Aging
CD-ROM	Compact disc read-only-memory
CFR	Code of Federal Regulations
CGIC	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity of Illness scale
CK	Creatine kinase
CMAI	Cohen-Mansfield Agitation Inventory
CNS	Central nervous system
CRO	Contract research organization
CSDD	Cornell Scale for Depression in Dementia
CSI	Caregiver Strain Index
CYP	Cytochrome P450
DM	Dextromethorphan
DPS	Dementia Progression Study
DSMB	Data and Safety Monitoring Board
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders
DX	Dextrorphan
ECDEU	Early Clinical Drug Evaluation Program
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EP	European Pharmacopeia
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase

Abbreviation	Definition
GMP	Good Manufacturing Practice
ICF	Informed consent form
ICH	International Conference on Harmonisation
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
MAOI	Monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent-to-Treat
MM	Medical Monitor
MMSE	Mini-Mental State Examination
MS	Multiple Sclerosis
NF	National Formulary
NIAAA	National Institute on Aging Alzheimer's Association
NINDS-ADRDA	National Institute of Neurological Disorders and Stroke – Alzheimer's Disease and Related Disorders Association
NMDA	*N*-methyl-D-aspartate
NPI	Neuropsychiatric Inventory
NPINH	Neuropsychiatric Inventory - Nursing Home version
OTC	Over–the-counter
PBA	Pseudobulbar affect
PET	Positron emission tomography
PGI-C	Patient Global Impression of Change
pH	Potential Hydrogen
PK	Pharmacokinetics
PR	The P-R interval from an ECG tracing
Q	Quinidine
QoL-AD	Quality of life Alzheimer's disease measure
QRS	The Q-R-S complex from an ECG tracing
QT	QT interval from an ECG tracing
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett's formula
QTcF	QT interval corrected for heart rate using the Fridericia's formula
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SERT	Serotonin transporter

Abbreviation	Definition
SIB	Severe Impairment Battery
SNRI	Serotonin-norepinephrine reuptake inhibitor
SOC	System organ class
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
TEAE	Treatment-emergent adverse event
USP	United States Pharmacopoeia
VGCC	Voltage-gated calcium channel
WBC	White blood cell

PROTOCOL AGREEMENT

Protocol Title:

A Phase 2, randomized, double-dummy, double-blind, placebo-controlled**,** 2-stage, sequential parallel study to assess the efficacy, safety, and tolerability of AVP-923 (dextromethorphan/quinidine) for the treatment of symptoms of agitation in patients with Alzheimer's disease.

Protocol Number: 12-AVR-131

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The signatures of the principal investigator and representative of the sponsor below constitute their approval of this protocol and further provide the necessary assurances that:

1. This study will be conducted according to Good Clinical Practice (GCP) and to all stipulations, as specified in both clinical and administrative sections of the protocol including the Declaration of Helsinki.
2. The conduct and results of this study will be kept confidential, and the electronic case report forms (eCRFs) and other pertinent data will become the property of Avanir Pharmaceuticals.
3. The protocol contains all necessary information required to conduct the study, as outlined in the protocol, and that the study will not be initiated without the approval of an appropriate Institutional Review Board (IRB).
4. All participants in this study will provide written informed consent in accordance with the requirements specified in the Code of Federal Regulations (21 CFR Parts 50, 56, 312) and/or the Declaration of Helsinki. All participants will also be informed that their medical records will be kept confidential except for review by Avanir or its representatives, the U.S. Food and Drug Administration (FDA), or other regulatory agencies if applicable.

Principal Investigator Signature Principal Investigator Name:	Date
Avanir Representative Signature Avanir Representative Name: Joao Siffert, MD	Date

STUDY SYNOPSIS

Title: A Phase 2, randomized, double-dummy, double-blind, placebo-controlled, 2-stage, sequential parallel study to assess the efficacy, safety, and tolerability of AVP-923 (dextromethorphan/quinidine) for the treatment of symptoms of agitation in patients with Alzheimer's disease.

Introduction

Alzheimer's disease (AD), the most common form of dementia, is a progressive neurodegenerative disease eventually leading to death. A recent review estimated that worldwide 24 million people have dementia, and that this number will double by the year 2020.[1] An estimated 5.4 million Americans have AD, this number has doubled since 1980 and is expected to be as high as 16 million by 2050.[2] Among US adults over age 65, prevalence estimates of dementia range from 5% to 15%, with AD being the most common type of dementia.[3-5]

AD is generally characterized by cognitive decline, impaired performance of daily activities, and behavioral disturbances.[6] Behavioral and psychiatric symptoms develop in as many as 60% of community-dwelling dementia patients[7,8] and in more than 80% of patients with dementia living in nursing homes;[9,10] the lifetime risk of such complications approaches 100%.[8,11,12] Frequent and severe dementia-related behavioral symptoms can be extremely distressing to the individual, the family, and caregivers. These behavioral disturbances have been associated with more rapid cognitive decline, institutionalization, and increased caregiver burden. Reduction or elimination of such disruptive agitated behaviors could therefore improve the ability of caregivers to manage patients at home, and perhaps postpone the need for institutionalization.[13,14]

Since there is no U.S. Food and Drug Administration (FDA)-approved treatment for dementia-related behavioral symptoms, prescribing of off-label antipsychotic drugs has been commonly employed to treat symptoms such as aggression and agitation.[15,16] Atypical antipsychotics have a modest effect in the short-term treatment of aggression (over 6–12 weeks) but only limited benefits in longer term therapy as adverse effects tend to offset potential efficacy.[17] Benefits are less well established for other symptoms such as agitation.[18] In addition, there are significant concerns over the potential for serious adverse outcomes with use of antipsychotic medications, including stroke and increased death rate.[19] Non-antipsychotic psychotropic medications have also been studied both for symptom mitigation and secondary prevention to little effect.[20] A careful consideration of other pharmacological and nonpharmacological approaches to treating agitation and aggression in patients with AD is, therefore, imperative.[21,22]

Rationale for Studying AVP-923 for Treatment for Agitation in Dementia

Dextromethorphan (DM) has a complex central nervous system (CNS) pharmacology and related neuroactive properties. It acts as a low-affinity uncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist[23-26] a high affinity sigma-1 receptor agonist,[27-29] and a voltage-gated calcium channel (VGCC) antagonist.[30,31] DM has also been shown to decrease potassium-stimulated glutamate release,[32] possibly via a sigma receptor-related mechanism.[33] Sigma-1 receptor

agonists modulate extracellular calcium influx, as well as intracellular calcium mobilization.[27] DM also binds with high affinity to the serotonin transporter (SERT) and inhibits serotonin reuptake.[34]

Although AVP-923 has not been specifically studied for agitation or other behavioral disturbances associated with dementia, preliminary data in pseudobulbar affect (PBA) patients suggest it may have a benefit. Combined, the pharmacology and preliminary clinical evidence suggest a potential benefit of AVP-923 in agitation and warrant further clinical testing in a controlled fashion.

Study Objectives

The objectives of the study are to evaluate the efficacy, safety, tolerability and pharmacokinetics (PK) of AVP-923 compared to placebo, for the treatment of symptoms of agitation in patients with AD.

Study Population

It is estimated that up to approximately 200 patients will participate in the study at approximately 30 to 40 centers in the US.

Eligible patients for this study must have a diagnosis of probable AD and must have clinically meaningful agitation secondary to AD.

Agitation is defined as a state of poorly organized and purposeless psychomotor activity characterized by at least one of the following types of behaviors:

- Aggressive verbal (e.g., screaming, cussing)
- Aggressive physical (e.g., destroying objects, grabbing, fighting)
- Non-aggressive physical (e.g., pacing)

Eligible participants must have symptoms of agitation (intermittently or constantly) within 7 days prior to screening and the agitation symptoms must be severe enough such that they interfere with daily routine and for which a prescription medication is deemed indicated, in the opinion of the treating physician.

Agitation will be further assessed using the Clinical Global Impression of Severity of Illness (CGI-S) scale (1-7). A score≥4 (moderately ill) on the CGI-S assessing agitation at screening and baseline is required for study participation.

Study Design

This is a multicenter, randomized, double-dummy, double-blind, placebo-controlled, 2-stage, sequential parallel study, consisting of 2 consecutive double-blind treatment stages (Stage 1 and Stage 2). Each stage is of 5-week duration.

Eligible patients will be randomly assigned at the Baseline visit to receive AVP-923 or matching placebo. Study medication will be administered orally twice-daily from Day 1 through Day 70. Screening procedures must occur within approximately 4 weeks prior to randomization. Following screening procedures for assessment of inclusion and exclusion criteria, and approval by the Medical Monitor (MM), eligible patients will be randomized into Stage 1 of the study. See Figure 2 for a detailed diagram of the study design.

Stage 1

Eligible patients will be randomized into Stage 1 of the study in a 3:4 (active:placebo) ratio to receive either AVP-923 capsules or matching placebo capsules administered orally for 5 consecutive weeks. To minimize bias, drug assignments will be modified randomly during the treatment period. Patients will have an approximately 70% chance of receiving AVP-923 at some point during the study. All patients receiving AVP-923 will start at AVP-923-20 (20 mg of DM and 10 mg of Q) once a day and be escalated up to AVP-923-30 (30 mg of DM and 10 mg of Q) BID. For the initial 7 days of the study, randomized patients will receive AVP-923-20 in the morning and placebo in the evening, or placebo twice-a-day (Stage 1, Days 1-7). Starting on Day 8, patients will receive AVP-923-20 twice-a-day or placebo twice-a-day for 2 consecutive weeks (Stage 1, Days 8-21), taking one capsule in the morning and one capsule in the evening, approximately 12 hours apart. On Day 22 of the study, the dose of study medication will be escalated in a double-blind manner. Patients receiving AVP-923-20 b.i.d. will increase to AVP-923-30 b.i.d., and patients receiving placebo b.i.d will continue receiving placebo for the remaining 2 weeks (Stage 1, Days 22-35) of the study.

All study medication including AVP-923-20 capsules, AVP-923-30 capsules and placebo capsules are of identical appearance in order to maintain the integrity of the blind.

Stage 2

Patients who have completed Stage 1 are eligible to participate in the 5-week Stage 2 of the study. Study medication will be administered orally twice daily throughout Stage 2.

Patients will be assigned to a double-blind treatment for additional 5 weeks as follows:

Patients who received AVP-923 in Stage 1 (Days 1-35), will receive AVP-923-30 b.i.d. for the entire 5-week duration of Stage 2 (Days 36-70).

Patients who received placebo in Stage 1 will be stratified into two sub-groups depending on their clinical response assessed by CGI-S scores of Agitation at Visit 4. Patients will be considered “responders” if their CGI-S score of Agitation is between 1 and 3 at Visit 4 (end of Stage 1) and their score in the Agitation/Aggression domain in the Neuropsychiatric Inventory (NPI) has decreased by 25% or greater compared to baseline. Patients who do not meet these criteria will be considered “non-responders”. Assessment of CGI-S and NPI at Visit 4 should be performed, whenever possible, by the same rater who has assessed CGI-S and NPI prior to randomization into Stage 1 of the study.

Each placebo sub-group (responders and non-responders) will then be re-randomized to receive either AVP-923 or matching placebo in a 1:1 ratio. Patients who received placebo during Stage 1 and are re-randomized to AVP-923 in Stage 2 will receive AVP-923-20 in the morning and matching placebo in the evening for the initial 7 days (Stage 2, Days 36-42) of the study. Starting on Day 43, patients will receive AVP-923-20 twice-a-day for 2 consecutive weeks (Stage 2, Days 43-56) and starting on Day 57 patients will receive AVP-923-30 b.i.d. for the remaining 2 weeks (Stage 2, Days 57-70) until study completion.

Those who are re-randomized to placebo in Stage 2 will receive placebo twice daily throughout Stage 2.

All study medication including AVP-923-20 capsules, AVP-923-30 capsules and placebo capsules are of identical appearance in order to maintain the integrity of the blind.

Assessments and Visits

Patients will attend clinic visits at Screening, Baseline (Day 1), and on Days 8, 22, 36, 43, 57, and 70 (Visits 2 – 7). Including the screening phase, the length of each patient's participation in this study will be approximately 14 weeks. Study procedures will be performed at each visit as outlined in the Schedule of Events (see Table 2). Blood samples for measurement of drug levels in plasma will be collected on Day 36 (Visit 4) and on Day 70 (Visit 7). A blood sample for cytochrome P450-2D6 (CYP2D6) genotyping will be collected on Day 1 (Baseline visit).

Statistical Design

Efficacy

As AVP-923 has not been specifically studied for treating behavioral disturbances in patients with dementia, preliminary data from which to base an assessment of the endpoint(s) that are most likely to demonstrate a beneficial effect of treatment (e.g. agitation) are not available. However, the Agitation/Aggression domain of the Neuropsychiatric Inventory (NPI) is pre-specified as the primary endpoint. Secondary efficacy measures include the total NPI, the Alzheimer's Disease Cooperative Study- Activities of Daily Living Inventory (ADCS-ADL), the Caregiver Strain Index (CSI), the Cornell Scale for Depression in Dementia (CSDD), the Patient Global Impression of Change (PGI-C), the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC), the Quality of Life-Alzheimer's disease measure (QoL-AD), and the changes in concomitant use of psychotropic drugs. It may be the case that one of these secondary endpoints may be a more appropriate endpoint for future studies. In addition, exploratory analysis of cognitive function will be assessed using the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog).

The primary and secondary efficacy endpoints are assessed in each of the two stages of the trial. For the primary efficacy analysis, as well as for all other efficacy analyses in which the data from the two stages are combined, the endpoint definition is based on both the change from Baseline to week 5 and on the change from the week 5 to week 10. Similarly, the analyses of the two

stages combined at other time points are based on combining the data from, for example, weeks 1 and 6, and weeks 3 and 8.

Safety

Safety will be assessed by reported adverse events (AEs), physical and neurological examinations, vital signs, clinical laboratory assessments, and electrocardiograms (ECGs).

Pharmacokinetic (PK) Analysis

PK results (DM, dextrorphan [DX], and quinidine [Q] plasma concentration data) will be summarized descriptively overall and by metabolizer group.

Data Safety Monitoring Board

The sponsor will appoint a Data and Safety Monitoring Board (DSMB) for the periodic review of available study data.

Sample Size Justification

Based on the analysis of published results of previously conducted clinical studies,[35-39] estimates of the standard deviation (SD) of the change from baseline in the NPI Agitation/Aggression score range from 3.1 to 5.2 points. Assuming an SD of 5.0 points, and based on the use of a two-sided, two-sample comparison of means from independent samples at the 5% level of significance, a total sample size of 196 patients (randomized in a 3:4 [AVP-923:placebo] ratio) will provide greater than 90% power to detect a mean difference of 2.5 points. However, the magnitude of the true treatment difference is unknown. If the treatment difference is 2.0 points, then the power to detect such a difference will be less than 75%. In addition, if the SD of the change from baseline in the NPI Agitation/Aggression score is larger than in prior studies, the power will be further reduced. As a result, this study should be considered to be an exploratory trial, the results of which will be used to design subsequent studies.

1 INTRODUCTION

Alzheimer's disease (AD), the most common form of dementia, is a progressive neurodegenerative disease eventually leading to death. A recent review estimated that worldwide 24 million people have dementia, and that this number will double by the year 2020.[1] An estimated 5.4 million Americans have AD, this number has doubled since 1980 and is expected to be as high as 16 million by 2050.[2] Among US adults over age 65, prevalence estimates of dementia range from 5% to 15%, with AD being the most common type of dementia.[3-5]

AD is generally characterized by cognitive decline, impaired performance of daily activities and behavioral disturbances.[6] Behavioral and psychiatric symptoms develop in as many as 60% of community-dwelling dementia patients[7,8] and in more than 80% of patients with dementia living in nursing homes;[9,10] the lifetime risk of such complications approaches 100%.[8,11,12] Frequent and severe dementia-related behavioral symptoms can be extremely distressing to the individual, the family, and caregivers. These behavioral disturbances have been associated with more rapid cognitive decline, institutionalization, and increased caregiver burden. Reduction or elimination of such disruptive agitated behaviors could therefore improve the ability of caregivers to manage patients at home, and perhaps postpone the need for institutionalization.[13,14]

Although behavioral disturbances are more frequent as the disease progresses, AD patients can manifest depression, disruptive behaviors (e.g., agitation, aggression) and psychosis at any stage of the disease.[12] This suggests that while some psychiatric symptoms are associated with the progressive nature of the disease, others result from specific phenotypes associated with increased vulnerability in specific brain areas. Frontal cortical circuits are particularly important in terms of aggression, psychosis, and agitation.[40-44]

A large cross-sectional study examined relationships among the constellation of psychiatric syndromes as a function of dementia severity in 1155 patients with probable AD.[45] Neuropsychiatric symptoms such as anxiety, wandering, irritability, inappropriate behavior, uncooperativeness, and emotional lability were found to be associated with agitation, aggression, and psychosis, which varied according to the severity of the dementia, suggesting a progressive deterioration of fronto-temporal limbic structures. Aggression was associated with agitation, uncooperativeness, and emotional lability in mild/moderate stages, and psychosis, uncooperativeness, and irritability in moderate/severe stages. As with aggression, agitation was also associated with frontal lobe symptoms in all stages of the disease, although this was more evident in mild/moderate stages.[45]

The longitudinal course of neuropsychiatric symptoms of dementia was studied at the population level in the community setting in the Cache County Study on Memory in Aging (CCSMHA) and Dementia Progression Study (DPS).[46,47] Of all permanent residents of Cache County, Utah who were 65 years or older in January, 1995, 5,092 (90%), were enrolled in the study. Those with suspected or probable dementia underwent a comprehensive assessment in the presence of a collateral informant. There were 432 participants with new-onset (i.e. incident) dementia in the CCSMHA, 408 of which were followed past 36 months. Sixty three percent of those had AD.

Neuropsychiatric inventory (NPI) assessments were performed at baseline and at follow up visits. Over 5 years, period prevalence for at least one neuropsychiatric symptom was 97% and was greatest for depression (77%), apathy (71%), and anxiety (62%). The frequency was also relatively high for neuropsychiatric symptoms such as agitation/aggression (~45%), irritability/lability (~68%), aberrant motor behavior (~55%), and disinhibition (~32%). The prevalence of neuropsychiatric symptoms tended to increase over time and about 25% of participants were treated with psychotropic drugs.[20]

Agitation is generally characterized by motor restlessness, a heightened response to stimuli, irritability, and inappropriate and often purposeless motor or verbal activity. Symptoms generally fluctuate over time, occasionally rapidly and are often associated with sleep disturbances.[48] Different attempts have been made to further classify subtypes of agitation. Cohen-Mansfield[49] distinguishes between the presence of an aggressive physical component (e.g., destroying objects, grabbing, fighting), and aggressive verbal component (e.g., screaming, cussing), a non-aggressive physical component (e.g., pacing), and a non-aggressive verbal component (e.g., continuous questioning).

Since there is no US Food and Drug Administration (FDA)-approved treatment for dementia-related behavioral symptoms, off-label prescribing of antipsychotic drugs has been commonly employed to treat symptoms such as aggression and agitation.[15,16] Atypical antipsychotics have a modest effect in the short-term treatment of aggression (over 6–12 weeks) but only limited benefits in longer term therapy as adverse effects tend to offset potential efficacy.[17] Benefits are less well established for other symptoms such as agitation.[18] In addition, there are significant concerns over the potential for serious adverse cardiovascular outcomes with use of antipsychotic medications, including stroke and increased death rate.[19] Non-antipsychotic psychotropics have been studied, both for symptom mitigation and secondary prevention, to little effect.[20] A careful consideration of other pharmacological and nonpharmacological approaches to treating agitation and aggression in patients with AD is, therefore, imperative. [21,22]

1.1 Rationale for Studying AVP-923 for Treatment for Agitation in Dementia

Dextromethorphan (DM) has a complex central nervous system (CNS) pharmacology and related neuroactive properties. It acts as a low-affinity uncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist,[23-26] a high affinity sigma-1 receptor agonist[27-29] and a voltage-gated calcium channel (VGCC) antagonist.[30,31] DM has also been shown to decrease potassium-stimulated glutamate release,[32] possibly via a sigma receptor-related mechanism.[33] Sigma-1 receptor agonists modulate extracellular calcium influx, as well as intracellular calcium mobilization. [27] DM also binds with high affinity to the serotonin transporter (SERT) and inhibits serotonin reuptake.[34]

Based on DM's pharmacology, AVP-923 clinical benefit in pseudobulbar affect (PBA), and preliminary clinical evidence for a potential benefit in agitation in patients with PBA, AVP-923 may also be efficacious in treating behavioral disturbances in patients with AD.

Accumulating clinical evidence suggests that NMDA antagonists may have an effect in controlling agitation in patients with dementia. Memantine, which is approved for the treatment of AD, also acts as a non-competitive, low potency NMDA receptor antagonist and inhibits prolonged cell influx of calcium ion.[50,51] A meta-analysis of data from the memantine efficacy trials was conducted to further examine the outcomes in AD patients who had agitation, aggression, or psychosis before entering the trials. Across the studies, improvement in the NPI behavioral symptom cluster was significantly better with memantine than with placebo at 3 and 6 months. Additionally, the incidence of discontinuations due to agitation was 3-fold higher in placebo treated patients than in patients receiving memantine.[52] A recent randomized, placebo controlled 12-week study assessed the potential effect of memantine in 153 nursing home patients with AD and agitation.[53] Whereas the primary endpoint, change in the Cohen-Mansfield Agitation Inventory (CMAI), failed to show a statistically significant difference from placebo, there were potential benefits suggested by improvements seen in the NPI (p=0.01) and AD-ADL (p=0.04). The severe impairment battery (SIB) also showed a cognitive effect favoring memantine (p=0.02). Another study conducted in community dwelling patients with moderate to severe AD receiving donepezil for at least 3 months (N=295) assessed the effects of various permutations of study medication-placebo, as follows: to continue donepezil, discontinue donepezil, discontinue donepezil and start memantine, or continue donepezil and start memantine. Patients received the study treatment for 52 weeks. The patients who received memantine, as compared with those who received placebo-memantine, had scores on the NPI that were lower (indicating fewer behavioral and psychological symptoms) by an average of 4.0 points (99% CI, 0.6 to 7.4; p=0.002). In contrast, donepezil did not have an effect on NPI scores).[54]

Additional evidence suggesting glutamate modulation as a potential therapeutic approach for the management of agitation and aggression in patients with dementia comes from studies using topiramate. This antiepileptic drug shares some of the known mechanisms of actions of other antiepileptic drugs (e.g. sodium conductance modulation) but also modulates glutamate by decreasing alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA)-kainate receptor mediated currents.[55] Fhager and colleagues (2003)[56] conducted a retrospective evaluation of 15 severely aggressive patients with dementia who did not respond to antipsychotic medication and then received topiramate either as monotherapy or added to an antipsychotic. Symptoms were rated using the CMAI at baseline and 2 weeks after initiating topiramate; patients in both groups showed a significant improvement in their aggressive behavior. In contrast, mibampator, a positive allosteric modulator of the glutamate AMPA receptor failed to show a benefit in a well controlled study of AD patients with agitation/aggression.[22]

Sigma-1 receptor mediated pharmacology may also play a role in dementia therapeutics and potentially in modulation of behavior. Pre-clinical studies have suggested that sigma-1 receptors are involved in many different diseases, including addiction, pain, mood disorders, psychosis, and AD, among others.[57] Animal studies studying potential neuroprotective and behavioral effects of donepezil suggest they can be related to modulation of sigma-1 receptors.[58-60] One study showed that PRE-084 or donepezil (non-selective sigma-1 agonists), when co-administered

with β_{25-35} to mice, blocked or attenuated the peptide-induced neurotoxicity. Neuroimaging studies in patients corroborate the potential involvement of sigma-1 receptors in AD pathology. Mishina et al., 2008,[61] reported a lower density of sigma-1 receptors in patients with AD compared to age-matched controls in a study using positron emission tomography (PET). Combined, these findings suggest that sigma-1 receptor modulation with DM may have potential beneficial effects in AD and related behaviors.

Lastly, although AVP-923 has not been specifically studied for agitation or other behavioral disturbances associated with dementia, preliminary data in patients with PBA suggest it may have a benefit. PBA itself can be considered a form of emotional lability and some authors classify emotional lability under the umbrella of syndromes described as "behavioral dysregulation and aggression," which includes emotional lability, agitation, and irritability, among other behaviors.[45] In fact, patients enrolled in the pivotal PBA study conducted by Avanir were assessed using the total NPI. At study entry, approximately 15% of study participants had scores in the agitation/aggression domain of the NPI that were in the moderate to severe range. A post-hoc exploratory and descriptive analysis of data from the 12-week, placebo-controlled Phase 3 study in patients with PBA secondary to MS or ALS[62] suggests a potential effect of AVP-923 on agitation. All patients were prospectively assessed with the NPI (a pre-specified secondary endpoint) at baseline and at study completion. Study participants were randomized into one of three groups: AVP-923-20 (20 mg of DM and 10 mg of Q; N=107), AVP-923-30 (30 mg of DM and 10 mg of Q; N=110), or placebo (N=109). At baseline, 14, 13, and 12 patients in the AVP-923-30, AVP-923-20, and placebo groups, respectively, had moderate/severe agitation as measured by the NPI "severity" scale. At study end, the number of patients with moderate/severe agitation was substantially lower in the AVP-923 groups (N=5 in each group) but higher in the placebo group (N=14).[62]

The FDA approved AVP-923-20 on October 2010, for the treatment of PBA (See Appendix 1) for full prescribing information).

Combined, the pharmacology and preliminary clinical evidence suggest a potential benefit of AVP-923 in agitation and warrant further clinical testing in a controlled fashion.

1.2 AVP-923 (dextromethorphan/quinidine)

1.2.1 Dextromethorphan

Because of its NMDA-receptor antagonism properties, several studies have investigated the treatment of neurological disorders with DM. In some of these trials, high doses of DM were administered in an attempt to maintain sufficient systemic levels of DM to overcome the degradative effect of first-pass metabolism by cytochrome P450 2D6 (CYP2D6). However, others have demonstrated that even at doses as high as 750 mg/day, DM is not detectable in the blood of some individuals.[63]

DM is extensively metabolized to dextrorphan (DX) and a number of other metabolites. The metabolic pathway involves *O*-demethylation and *N*-demethylation of DM leading to the formation of DX and 3-methoxymorphinan, respectively.[64]

DX and 3-methoxymorphinan undergo further demethylation to form 3-hydroxymorphinan. All of these metabolites are rapidly glucuronidated and are eventually eliminated as glucuronide and sulfate conjugates.[65]

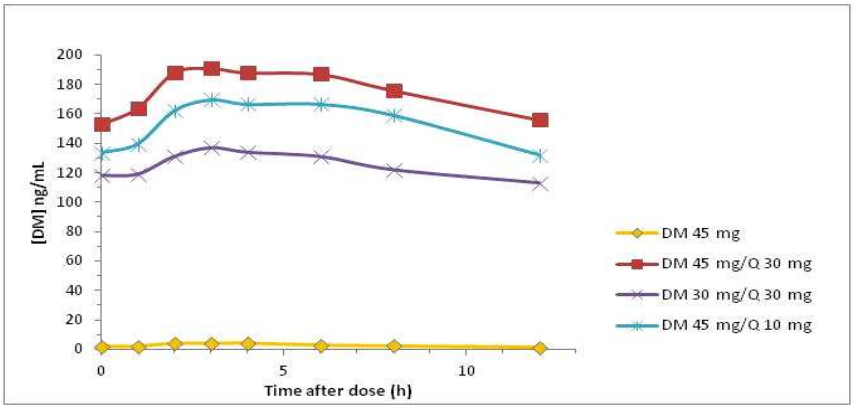
1.2.2 Effect of Quinidine on Metabolism of Dextromethorphan

When administered alone, DM has very low bioavailability in most individuals due to rapid CYP2D6-mediated first-pass liver metabolism in extensive metabolizers (approximately 90% of the general population are extensive metabolizers). This low bioavailability limits DM's therapeutic utility for chronic CNS disorders and may explain the inconsistent results observed in prior clinical studies, despite the relatively high doses utilized. A number of in vitro studies have been undertaken to determine the types of drugs that inhibit CYP2D6 activity. Quinidine (Q) is one of the most potent, predictable and well characterized of those that have been studied.[66]

These observations led to the hypothesis that concomitant dosing with Q could increase the DM plasma concentration of DM in vivo.

When combined with a low dose of Q, the bioavailability of DM is substantially increased. Figure 1 provides the plasma concentration versus time curves for various formulations of AVP-923 and DM alone. Administered as AVP-923, DM concentrations achieve plasma levels necessary for binding the various receptors believed to be relevant for DM pharmacology in CNS disorders.

Figure 1 DM Steady State Plasma Concentrations (Day 8)



Avanir Pharmaceuticals, Inc. Data on file: Data for DM 45 mg BID is from study 00-AVR-103; data for DM 45 mg/Q 30 mg is from study 07-AVR-125; data for DM 45 mg/Q 10 mg BID is estimated based on results from Study 07-AVR-125; data for DM 30 mg/Q 30 mg BID is from Study 04-AVR-116, using only data from healthy volunteers.

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1.3 Rationale for the Study Design

The randomized, placebo-controlled, double-dummy, double-blind, 2-stage, sequential parallel design is being adopted in an attempt to reduce sources of bias that are inherent to less well-controlled designs. A high response in the placebo-treated patients observed in countless studies of behavioral/psychiatric disorders, has been associated with negative results and constitutes a significant challenge for drug development.[67,68] The sequential parallel comparison design[67] selected for this study intends to overcome the potentially large placebo effect, by stratifying patients initially receiving placebo based on their clinical response in the first stage of the study.

The safety assessments used in this study are standard in clinical research and are generally recognized as reliable, accurate, and relevant. The rating scales used to assess efficacy are well-established instruments that are clinically validated and widely used in clinical studies of AD and other psychiatric and behavioral disorders.

1.4 Rationale for the Dose

The dose selection for the present protocol (12-AVR-131) was based on safety and efficacy data from a range of doses studied across several indications during AVP-923 clinical development. Doses of up to 60 mg DM with 60 mg Q have been administered to healthy volunteers and patients with a variety of neurological conditions including ALS, MS, AD, stroke, and traumatic brain injury. Doses planned for 12-AVR-131, AVP-923-20 and AVP-923-30, are expected to result in lower plasma concentrations for both DM and Q than the plasma concentrations observed with DM 30 mg/Q 30, the formulation most commonly employed in these clinical studies during AVP-923 development. DM mean C_{max} values for AVP-923-20 and AVP-923-30 are approximately 20% and 45% lower than the mean C_{max} values observed for DM 30 mg/Q 30 mg, respectively (based on calculations from studies 07-AVR-125 and 07-AVR-123). In addition, Q mean C_{max} values for Q are 70% lower following dosing with the new formulations containing only 10 mg Q.

The most common adverse events (AEs) observed across all studies are dizziness, headaches, and nausea; these AEs tended to ameliorate within a few weeks of dosing (Avanir data on file). Mild increases in QTc interval were also observed but a QTc >480 msec or changes in QTc >60 msec have been rare (Avanir data on file). The effects on QTc are primarily attributable to Q and are significantly smaller than those observed when Q is used at therapeutic doses to treat cardiac arrhythmias (600 – 1600 mg per day). Of the total number of patients with PBA treated with DM/Q (N = 363), 15% were ≥65 years with a maximum age of 82 years. Clinical studies of DM/Q did not include sufficient number of subjects aged 65 and over to determine whether they respond differently than younger subjects; however, a population PK analysis of 170 subjects (148 subjects <65 years old and 22 subjects ≥65 years old) in the controlled studies of patients with PBA revealed similar PK between those <65 years and those ≥65 years of age.

The incidence of any TEAE in patients who received any dose of the AVP-923 combination in the controlled studies in patients with PBA was similar for subjects aged less than 65 years (88.5%) and for subjects aged ≥65 years (90.6%). The incidence of TEAEs in common AE

categories, such as GI disorders and nervous system disorders, was also similar in the 2 age groups, as was the incidence of common TEAEs, including diarrhea, nausea, weakness, and dizziness. In all studies conducted in patients with PBA, the incidence of SAEs was higher for subjects treated with any dose of AVP-923 aged ≥65 years (33.6%) than for those aged less than 65 years (20.8%). However, the incidence of SAEs was also higher for patients treated with placebo aged≥65 years (23.5%) than for those aged less than 65 years (6.0%). The increased percentage of SAEs in the elderly population reflects the increased co-morbidities associated in this population. Overall, there were no major differences in safety profile of AVP-923 between patients <65 years of age and those ≥65 years of age (Avanir data on file).

In the placebo-controlled, pivotal study for the treatment of symptoms of PBA, AVP-923-20 and AVP-923-30 showed statistically significant efficacy and clinically meaningful relief, while appearing to be safe and well tolerated in the overall study population of patients with MS and ALS. Although this study was not powered to detect a difference between the two dose levels, and although there was no dose-related differences in the primary efficacy outcome measure, several pre-specified efficacy measures showed a statistically significant advantage of AVP-923-30 over AVP-923-20, suggesting a dose response relationship (Avanir data on file). In addition, PK/PD analyses showed that DM exposure is directly correlated with PBA improvement.

In summary, the dose combinations included in this study (AVP-923-20 and AVP-923-30) and the dose escalation regimen as proposed are expected to achieve sustained and sufficient plasma levels of DM to potentially provide therapeutic benefit while minimizing possible safety concerns in this elderly population with AD.

1.5 Rationale for the Duration of Dosing

Previously conducted studies with AVP-923 for the treatment of PBA have shown rapid onset of effect and clinically meaningful benefit over time. PBA patients with ALS and MS receiving AVP-923 have shown significant efficacy after 1 week of treatment with greater and sustained effect for up to 24 weeks in well controlled and open-label studies (Avanir data on file).

Several previously conducted well controlled studies for the treatment of agitation and aggression in different medical conditions, including AD, have been between 4 and 12 weeks duration.[69-72] Available data from PBA studies with AVP-923 and published research experience for this indication support that the proposed dosing scheme and duration in this study is sufficient to initially determine the efficacy of AVP-923 and its safety profile in the treatment of agitation secondary to AD.

2 Objectives

The primary objective of the study is to evaluate the efficacy of AVP-923 compared to placebo, for the treatment of symptoms of agitation in patients with AD.

The secondary objectives of the study are to evaluate the safety, tolerability, and pharmacokinetics (PK) of AVP-923 (AVP-923-20 and AVP-923-30) in patients with AD.

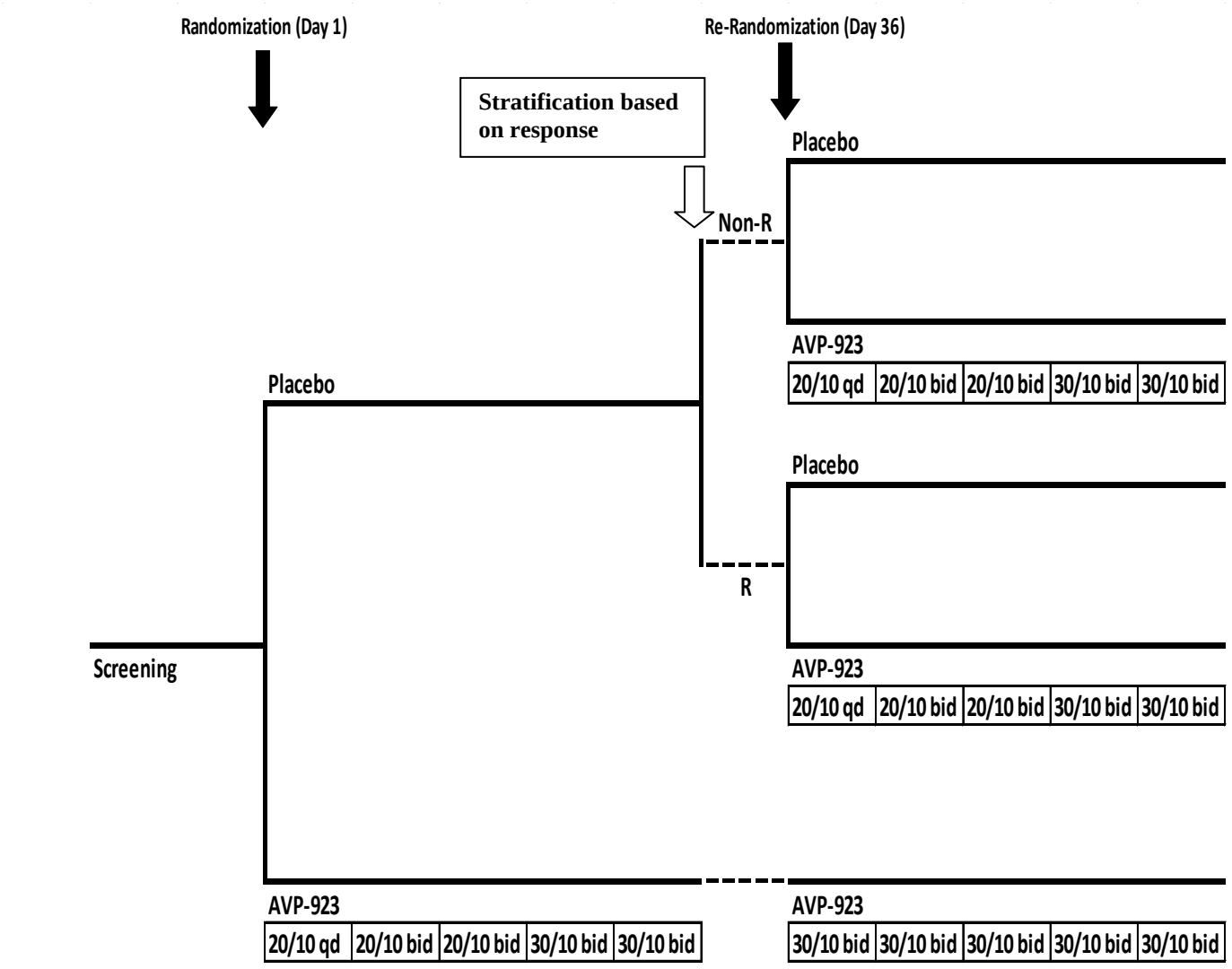
3 Study Design

This is a multicenter, randomized, double-dummy, double-blind, placebo-controlled, 2-stage, sequential parallel study, consisting of 2 consecutive double-blind treatment stages (Stage 1 and Stage 2). Each stage is of 5-week duration. (See Figure 2 - Study Schematic)

Up to approximately 200 patients will be enrolled at approximately 30 to 40 centers in the US.

Eligible patients will be randomly assigned at the Baseline visit to receive AVP-923 or matching placebo. Study medication will be administered orally twice-daily from Day 1 through Day 70. The first dose of study medication will be administered in the clinic on Day 1 (Baseline visit) and the morning dose of study medication will also be administered in the clinic on Day 36 (Visit 4) and Day 70 (Visit 7). On all other days, the caregiver can administer study medication or supervise the patient in self-administration of study medication without regard to clinic visit. Screening procedures must occur within approximately 4 weeks prior to randomization. Following screening procedures for assessment of inclusion and exclusion criteria, eligible patients will be randomized into Stage 1 of the study.

Figure 2 Study Schematics



Period	Screening		Stage 1					Stage 2				
Visit			B	V2		V3		V4	V5		V6	V7
Day	-28	-7	1 7	8 14	21	22 28	35	36* 42	43 49	56	57 63	70
Week	Week -4	Week -1	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10

R: Placebo Responder

Non-R: Placebo Non-Responder

B: Baseline Visit

*: Visit 4 (Stage 2) will occur after efficacy has been evaluated. Re-randomization will occur after CGI-S and NPI scores have been entered in the IWRS.

Stage 1

Eligible patients will be randomized into Stage 1 of the study in a 3:4 (active:placebo) ratio to receive either AVP-923 capsules or matching placebo capsules administered orally for 5 consecutive weeks. For the initial 7 days of the study, randomized patients will receive AVP-923-20 and placebo in the evening, or placebo twice-a-day (Stage 1, Days 1-7). Starting on Day 8, patients will receive AVP-923-20 twice-a-day or placebo twice-a-day for 2 consecutive weeks (Stage 1, Days 8-21), taking one capsule in the morning and one capsule in the evening, approximately 12 hours apart. On Day 22 of the study the dose of study medication will be escalated in a double-blind manner; patients receiving AVP-923-20 b.i.d. will start receiving AVP-923-30 b.i.d., and patients receiving placebo b.i.d will continue receiving placebo b.i.d. for the remaining 2 weeks (Days 22-35) of Stage 1 of the study.

All study medication including AVP-923-20 capsules, AVP-923-30 capsules and placebo capsules are of identical appearance in order to maintain the integrity of the blind.

Stage 2

Patients who have completed Stage 1 are eligible to participate in the 5-week Stage 2 of the study. Study medication will be administered orally twice daily throughout Stage 2.

Patients will be assigned to a double-blind treatment for additional 5 weeks as follows:

Patients who received AVP-923 in Stage 1 (Days 1-35), will receive AVP-923-30 b.i.d. for the entire 5-week duration of Stage 2 (Days 36-70).

Patients who received placebo in Stage 1 will be stratified into two sub-groups depending on their clinical response assessed by CGI-S scores of Agitation at Visit 4. Patients will be considered “responders” if their CGI-S score of Agitation is between 1 and 3 at Visit 4 (end of Stage 1) and their score in the Agitation/Aggression domain in the NPI has decreased by 25% or greater compared to baseline. Patients who do not meet these criteria will be considered “non-responders”. Assessment of CGI-S and NPI at Visit 4 should be performed, whenever possible, by the same rater who has assessed CGI-S and NPI prior to randomization into Stage 1 of the study.

Each placebo sub-group (responders and non-responders) will then be re-randomized to receive either AVP-923 or matching placebo in a 1:1 ratio. Patients who received placebo during Stage 1 and are re-randomized to AVP-923 in Stage 2 will receive AVP-923-20 in the morning and matching placebo in the evening for the initial 7 days (Stage 2, Days 36-42) of the study. Starting on Day 43, patients will receive AVP-923-20 twice-a-day for 2 consecutive weeks (Stage 2, Days 43-56) and on Day 57, patients will receive AVP-923-30 b.i.d for the remaining 2 weeks (Stage 2, Days 57-70) until study completion.

Those who are re-randomized to placebo in Stage 2 will receive placebo twice daily throughout Stage 2.

All study medication including AVP-923-20 capsules, AVP-923-30 capsules, and placebo capsules are of identical appearance in order to maintain the integrity of the blind.

4 Study Population

It is estimated that up to approximately 200 patients will participate in the study at approximately 30 to 40 centers in the US.

Eligible patients for this study must have a diagnosis of probable AD and must have clinically meaningful agitation secondary to AD.

The diagnosis of probable AD will be based on the 2011 Diagnostic Guidelines for Alzheimer's Disease issued by the National Institute on Aging (NIA)-Alzheimer's Association (AA) workgroups.[73] These new criteria were developed with basis on the review the National Institute of Neurological Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINDS–ADRDA) criteria.[74] Neither AD nor agitation should be explainable by delirium or major psychiatric disorders.

Agitation is defined as a state of poorly organized and purposeless psychomotor activity characterized by at least one of the following types of behaviors:

- Aggressive verbal (e.g., screaming, cussing)
- Aggressive physical (e.g., destroying objects, grabbing, fighting)
- Non-aggressive physical (e.g., pacing)

Eligible participants must have had symptoms of agitation (intermittently or constantly) within 7 days prior to screening and the agitation symptoms must be severe enough such that they interfere with daily routine and for which a prescription medication is deemed indicated, in the opinion of the treating physician.

Agitation will be further assessed using the Clinical Global Impression of Severity of Illness (CGI-S) scale (1-7). A score≥4 (moderately ill) on the CGI-S assessing agitation at screening and baseline is required for randomization into Stage 1.

Eligible patients are to have otherwise acceptable and stable general health as required by the study protocol, and documented by medical history, physical examination, electrocardiogram (ECG), and clinical laboratory examinations.

Eligible patients must have a caregiver that is able and willing to comply with all required study procedures, ensuring that the patient attends all study visits and takes the study medication as instructed. Caregivers will also be instructed to keep a study diary, to report any changes in patient's status, including adverse events, standard of care setting (e.g., becoming a resident in an assisted living facility), and to provide their impression and assessment regarding the investigational treatment. In order to qualify as a caregiver for this study, the individual should spend time with the patient for a minimum of 4 hours on 4 separate days per week.

Participants' caregivers must provide a signed informed consent form (ICF) for the procedures in this study protocol.

4.1 Inclusion Criteria

1) Males and females 50 to 90 years of age, inclusive.

2) Diagnosis of probable AD according to the 2011 NIA-AA working groups criteria.[73]

3) Either out-patients or residents of an assisted-living facility or a skilled nursing home.

4) The patient has clinically significant symptoms of agitation (Section 4 defines agitation), within 7 days prior to screening, that interfere with daily routine activities and for which a prescription medication is deemed indicated, in the opinion of the investigator.

5) CGI-S score assessing Agitation is ≥4 (moderately ill) at screening and baseline.

6) Mini-Mental State Examination (MMSE) score at screening is between 8 and 28 (inclusive).

7) The patient has stable cardiac, pulmonary, hepatic, and renal function.

8) The patient has an ECG (obtained within the past month prior to randomization and evaluated by a central ECG reader) with no evidence of complete heart block, ventricular tachycardia, or frequent unifocal ventricular ectopic beats (>5 per minute).

9) If female of childbearing age, must have been practicing a medically-acceptable method of birth control for at least 1 month prior to randomization and continue with the same method during the entire study duration (oral contraceptive tablets, hormonal implant device, hormone patch, intrauterine device, diaphragm and contraceptive cream or foam, condom with spermicide, or abstinence) or be surgically sterile or post-menopausal.

10) Patients currently receiving a drug for the treatment of AD (e.g., donepezil, rivastigmine, galantamine, memantine) are eligible provided they have been on a stable dose of these medications for at least 2 months prior to randomization.

11) Concomitant use of antidepressants such as SSRIs (e.g., fluoxetine, sertraline, citalopram), SNRIs (e.g., venlafaxine, desvenlafaxine, duloxetine) are allowed, provided the dose has been stable for at least 1 month prior to randomization. Paroxetine, a CYP2D6 substrate, is allowed provided the dose does not exceed 10 mg/day.

12) Patients currently taking allowed medications for the treatment of agitation secondary to AD (e.g., antipsychotics, buspirone) are eligible provided they have been on a stable dose for at least 1 month prior to randomization.

13) Concomitant use of the following medications for nighttime management of insomnia or behavioral disturbances, provided the dose and regimen have been stable for at least 1 month prior to randomization and remain stable throughout the study, is allowed.

a. Allowed medications for nighttime management of insomnia or behavioral disturbances (to be administered in the evening or at bedtime only):

- Short acting benzodiazepines (e.g., midazolam, oxazepam, brotizolam, triazolam)
- Low dose of alprazolam up to 0.5 mg/day
- Low dose of trazodone up to 50 mg/day

14) Patient must not show current and significant symptoms of a depressive disorder and must have a score <10 in The Cornell Scale for Depression in Dementia (CSDD) at Screening.

15) Patient must have no history or current clinical symptoms of schizophrenia, schizoaffective disorder, or bipolar disorder, as defined in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR).

16) Caregiver must be willing to comply with study procedures, including not administering any prohibited medications during the course of the study.

17) Caregiver signed and received a copy of a caregiver's ICF after the nature and risks of study participation had been fully explained to them.

18) Patients who are capable of providing assent but not capable of signing the ICF, according to the investigator, should provide assent for study participation.

a. Patients who sign the ICF are not required to provide a separate assent.

b. Patients who are not capable of providing assent are still allowed to participate provided the patient's authorized representative agrees to participation. Investigators must document the reasons for any patient that is unable to provide assent and maintain this documentation with the consent/assent documents.

19) Patients who are capable, according to the investigator, or patient's authorized representative signed and received a copy of a patient's ICF after the nature and risks of study participation had been fully explained to them.

4.2 Exclusion Criteria

1. Caregiver is unwilling or unable, in the opinion of the investigator, to comply with study instructions.
2. Patient has other type of dementia (e.g., vascular dementia, frontotemporal dementia, Parkinson's disease, substance-induced dementia).
3. Patient is hospitalized in a mental health facility (e.g., psychiatric hospital or ward).
4. Patient with symptoms of agitation that are not secondary to AD (e.g., pain, other psychiatric disorder or delirium due to a metabolic disorder, systemic infection or substance-induced).
5. Patients with myasthenia gravis.

6. Patients with any personal history of complete heart block, QTc prolongation, or *torsades de pointes*.

    b. Screening QTcB or QTcF of >450 msec for males and >470 msec for females based on central review unless due to ventricular pacing

7. Patients with any family history of congenital QT interval prolongation syndrome.
8. Patients with known hypersensitivity to DM, Q, opiate drugs (codeine, etc.), or any other ingredient of the study medication.
9. Patients with history of allergy to benzodiazepines (e.g., lorazepam).
10. Patients who have received DM co-administered with Q at any time in the past.
11. Patients who have been taking disallowed concomitant medications (See Section 5.5.3) within 2 weeks or 5 half-lives, whichever is longer prior to Baseline (Day 1).
12. Patients with co-existent clinically significant or unstable systemic diseases that could confound the interpretation of the safety results of the study (e.g., malignancy [except skin basal-cell carcinoma or untreated prostate cancer], poorly controlled diabetes, poorly controlled hypertension, unstable pulmonary, renal or hepatic disease, unstable ischemic cardiac disease, dilated cardiomyopathy, or unstable valvular heart disease). Certain other non-metastatic cancer may be allowed. Each case to be evaluated individually with the MM.
13. Patients who are currently participating in, or who have participated in other interventional (drug or device) clinical study within 30 days of baseline.
14. Patients with history of postural syncope, or any history of unexplained syncope (evaluated on a case by case basis) within 12 months of baseline.
15. Patients with a history of substance and/or alcohol abuse within the past 3 years.

4.3 Patient Withdrawal

Patients and caregivers will be advised verbally and in the written ICF that they have the right to withdraw from the study at any time without prejudice or loss of benefits to which they are otherwise entitled. The investigator or sponsor may discontinue a patient from the study in the event of an intercurrent illness, adverse event, other reasons concerning the health or well-being of the patient, or in the case of lack of cooperation, non-compliance, protocol violation, or other administrative reasons. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request the caregiver return all unused investigational product) (IP), and follow-up with the patient regarding any unresolved adverse events.

In addition, patients who present a QTc interval (QTcB or QTcF) >500 msec (unless due to ventricular pacing) or a QTc interval change from the screening ECG of >60 msec at any time after randomization, will be withdrawn from the study. The QTc values will be assessed for clinical significance and recorded.

Patients who withdraw prior to study completion will be asked to return to the clinic to complete the Visit 7 (End of Study) assessments.

If the patient withdraws from the study, and consent is withdrawn by the caregiver and/or patient's representative for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Patients who withdraw from the study will not be replaced.

5 Study Treatments

5.1 Treatments Administered

5.1.1 Description of Study Medications

Clinical study medication will be provided as hard, gelatin capsules (size 1). Each capsule of the study medication contains 1 of the following:

Treatment A: AVP-923-20 (20 mg of DM [USP, EP] and 10 mg of Q [USP, EP])

Treatment B: AVP-923-30 (30 mg of DM [USP, EP] and 10 mg of Q [USP, EP])

Treatment C: Placebo, with the same excipients as the study medication

Drug supplies will be provided to the site in double-blind, individually packaged, pre-labeled containers.

All medication used in this study will be prepared, packaged, and labeled in accordance with Good Manufacturing Practice (GMP) guidelines, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable laws and regulations.

5.1.2 Composition of AVP-923

The composition of the 2 doses of the IP is listed in Table 1.

Table 1 Composition of Investigational Product

Ingredient (amounts in mg)	AVP-923-30	AVP-923-20	Placebo
Dextromethorphan hydrobromide USP, EP	30.00	20.00	0
Quinidine sulfate dihydrate USP, EP	10.00	10.00	0
Croscarmellose sodium NF	7.80	7.80	7.80
Microcrystalline cellulose NF	94.00	94.00	94.00
Colloidal silicone dioxide NF	0.65	0.65	0.65
Lactose monohydrate NF	116.90	126.90	156.90
Magnesium stearate NF	0.65	0.65	0.65

EP = European Pharmacopoeia; USP = United States Pharmacopoeia; NF = National Formulary

5.1.3 Packaging

The investigators will be supplied with the IP packaged in kits containing two 85cc white plastic bottles with child-resistant caps, one bottle with white label for the morning dosing and one bottle with blue label for the evening dosing. Each bottle will contain 18 capsules of AVP-923-

30 (dextromethorphan hydrobromide 30 mg/quinidine sulfate 10 mg), AVP-923-20 (dextromethorphan hydrobromide 20 mg/quinidine sulfate 10 mg), or identically-appearing placebo. Each kit is comprised of two 18-count bottles containing enough study medication for 2 weeks of treatment.

5.1.4 Labeling

All labels will contain product name, protocol number, material ID number, an investigational drug warning, dosage instructions to take one capsule in the morning or in the evening as appropriate, storage conditions, lot number, and company name. The kit label will consist of 2-panels, with one detachable panel that will be removed and affixed to the study medication Dispensing Log page at the time of dispensing. Space is provided on both panels of the kit label to record patient number and initials, the site number and dispensing date. On the bottle labels space is provided to record patient no. and dispensing date, before the kit is dispensed to the patient. All investigational product labels comply with all applicable federal and local regulations.

5.1.5 Storage of Clinical Supplies

Clinical supplies must be stored in compliance with label requirements in a secure place and kept at room temperature; 25°C (77°F) with excursions permitted to 15°C to 30°C (59°F-86°F).

5.1.6 Study Medication Administration

All patients will receive AVP-923 or matching placebo according to the kit number assigned by an interactive web response system (IWRS) randomization scheme. Designated staff at each site will dispense study medication. The caregiver will administer study medication or supervise the patient in self administration of the study medication, except at the Baseline Visit (Day 1), Visit 4 (Day 36), and Visit 7 (Day 70) when patients will be administered their dose of study medication from the white label bottle at the clinic in the presence of site personnel regardless of time of day. Patients and caregivers will be instructed that the patient should take the study medication approximately every 12 hours ± 4 hours orally with water (morning and evening). Patient's caregiver will record the time the patient takes each dose of medication in the diary card. Patient's missed doses will be noted in the electronic case report form (eCRF).

Stage 1: At Baseline Visit (Day 1), Visit 2 (Day 8), and Visit 3 (Day 22), study medication will be dispensed and administered as follows:

- Baseline Visit (Day 1): AVP-923-20 or Placebo; caregivers will be dispensed one kit containing two bottles, one bottle with a white label for the morning dosing and one bottle with a blue label for the evening dosing. Patients will be administered one capsule from the white label bottle in the morning and one capsule from the blue label bottle in the evening, approximately 12 hours apart for 7 days.

- Visit 2 (Day 8): AVP-923-20 or Placebo; caregivers will be dispensed one kit containing two bottles, one with a white label for the morning dosing and one bottle with a blue label for the evening dosing. Patients will be administered one capsule from the white label bottle in the morning and one capsule from the blue label bottle in the evening, approximately 12 hours apart for 14 days.
- Visit 3 (Day 22): AVP-923-30 or Placebo; caregivers will be dispensed one kit containing two bottles, one with a white label for the morning dosing and one bottle with a blue label for the evening dosing. Patients will be administered one capsule from the white label bottle in the morning and one capsule from the blue label bottle in the evening, approximately 12 hours apart for 14 days.

Stage 2: At Visit 4 (Day 36), Visit 5 (Day 43), and Visit 6 (Day 57), study medication will be dispensed and administered as follows:

- Visit 4 (Day 36): AVP-923-20 or AVP-923-30 or Placebo; caregivers will be dispensed one kit containing two bottles, one bottle with a white label for the morning dosing and one bottle with a blue label for the evening dosing. Patients will be administered one capsule from the white label bottle in the morning and one capsule from the blue label bottle in the evening, approximately 12 hours apart for 7 days.
- Visit 5 (Day 43): AVP-923-20 or AVP-923-30 or Placebo; caregivers will be dispensed one kit containing two bottles, one with a white label for the morning dosing and one bottle with a blue label for the evening dosing. Patients will be administered one capsule from the white label bottle in the morning and one capsule from the blue label bottle in the evening, approximately 12 hours apart for 14 days.
- Visit 6 (Day 57): AVP-923-30 or Placebo; caregivers will be dispensed one kit containing two bottles, one with a white label for the morning dosing and one bottle with a blue label for the evening dosing. Patients will be administered one capsule from the white label bottle in the morning and one capsule from the blue label bottle in the evening, approximately 12 hours apart for 14 days.

All study medication will be supplied and administered in a double-blind manner throughout the entire duration of the study.

5.2 Accountability of Study Supplies

5.2.1 Receipt of Supplies

The investigator is responsible for maintaining an inventory of each shipment of IP received and comparing it with the accompanying Drug Accountability Report/Material Shipping Form. The investigator will verify the accuracy of the information on the form, sign and date it, and return the form to the sponsor or its representative. All IP supplied is for use only in this study and should not be used for any other purpose. All kit numbers will also be recorded and tracked at the site using the Drug Accountability Log.

5.2.2 Record of Dispensing

Accurate recording of all IP dispensing for individual patients will be made in the appropriate section of the patient's eCRF. This eCRF will contain the following information: (i) the initials and patient number to whom the drug was dispensed; (ii) the date(s) and quantity of the drug dispensed to the patient; and (iii) the kit number assigned to the patient via IWRS.

Additionally, the detachable panel of the two-panel label on each kit will be removed and affixed to the study medication Subject Drug Dispensing Log page at the time of dispensing. Space is provided on both panels of the kit label to record patient number and initials, the site number and dispensing date.

5.2.3 Unused Supplies

At the end of the study, all unused investigational supplies must be inventoried on the Drug Accountability Log and returned to the sponsor or its representative, along with a completed and signed Drug Accountability Report/Material Shipping Form. If any study medication is lost or damaged, it should be indicated on the form.

5.3 Methods of Assigning Patients to Treatment Groups

5.3.1 Randomization

Upon entry into the study (after ICF is signed at screening), all patients will be assigned a 6-digit patient number. The first 3 digits consist of the center number. The last 3 digits will be assigned sequentially starting with 001. This 6-digit number is the main identifier for patients.

Eligible patients will be randomized to receive either AVP-923 or placebo on Day 1 (Baseline, Stage 1) in a double-blind manner according to a randomization scheme devised by Avanir or its representative and managed within an IWRS. The randomization will be stratified by cognitive function (high vs. low) and severity of agitation (moderate vs. severe) at Baseline. Blocked randomization is used to ensure treatment balance in each stratum. Dynamic allocation will be handled by IWRS by dynamically assigning the blocks to centers as they are needed.

The re-randomization on Day 36 (Visit 4, Stage 2) will be conducted in a similar fashion. The patient number will not be re-assigned; it will remain the same in both stages of the study.

5.3.2 Blinding/Masking

Blinding will be maintained by providing capsules of the 2 doses of AVP-923 and placebo that are identical in appearance. Neither the sponsor, patients, caregivers, investigators, nor other study personnel will be aware of a patient's treatment assignment. In the event that it becomes medically necessary to identify which treatment a patient has received, the blind can be broken. In that event, the investigator is to contact Avanir's MM or representative to request the

unblinding of a patient. The IWRS manager is not required to be blinded and he or she will have access to the study medication list and the randomization code.

5.4 Patient Compliance

Patients and caregivers will be instructed to bring any unused study medication and empty containers to the clinic on Days 8, 22, 36, 43, 57, and 70 (Visits 2 – 7). For this study, compliance will be defined as when a patient takes at least 80% of their scheduled doses. Caregivers will be provided with diary cards and will be instructed to record daily the number of capsules taken and the time of administration. Diary cards will be collected on Days 8, 22, 36, 43, 57, and 70 (Visits 2-7), or at the time of early study discontinuation.

5.5 Concomitant Medication

Patients may not take any of the disallowed medications listed in Section 5.5.3 during the study or 2 weeks or 5 half-lives, whichever is longer, prior to the start of dosing on Day 1. At each visit, caregivers will be queried as to whether or not the patient has taken any concomitant medications and, if so, the investigator will record the medications taken and the reasons for their use. Caregivers will be instructed to record concomitant use of rescue medication (Lorazepam) in the diary.

5.5.1 Allowed Concomitant Medications

Drugs for the treatment of AD (e.g., donepezil, rivastigmine, galantamine, memantine) are allowed when administered at stable dose for at least 2 months prior to randomization; the dose of these drugs should remain unchanged throughout the study. If dose adjustment is necessary, the new dose and the reason for the change should be recorded.

The use of drugs for the treatment of agitation secondary to AD (e.g., atypical antipsychotics, butyrophenones, buspirone) is allowed, provided the patient has been on a stable dose for at least 1 month prior to randomization and throughout the study.

Concomitant use of the following medications for nighttime management of insomnia or behavioral disturbances, provided the dose and regimen have been stable for at least 1 month prior to randomization and remain stable throughout the study, is allowed.

- Allowed medications for nighttime management of insomnia or behavioral disturbances (to be administered in the evening or at bedtime only):
    1. Short acting benzodiazepines (e.g., midazolam, oxazepam, brotizolam, triazolam)
    2. Low dose of alprazolam up to 0.5 mg/day
    3. Low dose of trazodone up to 50 mg/day

All other benzodiazepines are disallowed, except for lorazepam use for short term treatment of agitation (See Section 5.5.2).

Concomitant use of hypnotics (e.g., eszopiclone, zolpidem, zaleplon) for the treatment of insomnia is allowed, provided the dose has been stable for at least 1 month prior to randomization and remains stable throughout the study.

Concomitant use of antidepressants such as SSRIs (e.g., fluoxetine, sertraline, citalopram), SNRIs (e.g., venlafaxine, desvenlafaxine, duloxetine) are allowed, provided the dose has been stable for at least 1 month prior to randomization. Paroxetine, a CYP2D6 substrate, is allowed provided the dose does not exceed 10 mg/day. SSRIs, SNRIs and paroxetine must remain stable throughout the study unless a dose reduction is deemed necessary for management of an adverse event.

5.5.2 Rescue Medication for the Symptoms of Agitation

Patients will be allowed to receive oral lorazepam as rescue medication for the short-term treatment of symptoms of agitation if deemed necessary by the investigator. Lorazepam will be administered in a dose up to 1.5 mg/day and not to exceed 3 days in a 7-day period. Caregivers must record concomitant use of lorazepam in the diary.

5.5.3 Disallowed Concomitant Medications

Patients who are currently taking, or have taken any of the following drugs, within **2 weeks or 5 half-lives, whichever is longer,** prior to the initiation of the study medication administration, are to be excluded:

Drugs that may increase Q levels (exclusion does not include topical medications unless applied under occlusive dressing or other technique that is intended to increase systemic absorption)**:**

- Ketoconazole
- Itraconazole
- Voriconazole
- Carbonic anhydrase inhibitors
- Amiodarone
- Cimetidine
- Diltiazem
- Verapamil
- Protease inhibitors (e.g., saquinavir, ritonavir, atazanavir, indinavir)
- Macrolide antibiotics (e.g., erythromycin, azythromycin, clarithromycin, dirithromycin, roxithromycin)

Drugs that may have increased plasma levels if co-administered with Q:

- Tricyclic antidepressants (TCA; e.g., imipramine, desipramine, amitriptyline, nortriptyline)
- Quinidine
- Dextromethorphan (over-the-counter [OTC] and prescription)

Drugs that are related to Q:

- Quinine
- Mefloquine

Drugs that may produce serotonin syndrome when co-administered with DM:

- Monoamine oxidase inhibitors (MAOIs)
  - Patients should allow at least 14 days after stopping study medication before starting an MAOI

Drugs that may decrease DM and Q plasma levels:

- St. John's Wort
- Hyperforin
- Rifampicin
- Phenytoin
- Carbamazepine
- Oxcarbazepine
- Phenobarbital
- Cyproterone

Drugs that may be prescribed for the treatment of agitation:

- Phenothiazines (thioridazine, trifluoperazine, chlorpromazine, promazine, perphenazine, methotrimeprazine, fluphenazine)

6 Study Assessments and Procedures

6.1 Pharmacokinetics (PK)

At Day 36 (Visit 4) and Day 70 (Visit 7) patients will have a blood sample collected between 0 – 3 hours after the morning dose of study medication for analysis of DM, DX, and Q plasma levels. The time when the patient was administered the dose of study medication and the time of the blood draw will be recorded on the eCRF. Plasma samples will be separated by centrifugation and then frozen at -20° C until assayed at the analytical unit.

6.2 Efficacy

Examples of all the scales and questionnaires that will be used during the study can be found in the Appendices.

6.2.1 Clinical Global Impression of Severity of Illness (CGI-S)

The CGI-S (Appendix 2) is an observer-rated scale that measures illness severity and is one of the most widely used brief assessment tools in psychiatry research.

The Early Clinical Drug Evaluation Program (ECDEU) version of the CGI-S included in this protocol is the most widely used format of this validated tool, and asks that the clinician rate the patient relative to their past experience with other patients with the same diagnosis, with or without collateral information. The CGI-S has proved to be a robust measure of efficacy in many clinical drug trials,[75-79] and is easy and quick to administer, provided that the clinician knows the patient well.[80]

Reliability and validity of CGI have been tested in multiple studies, including patients with dementia, schizophrenia and affective disorders. Overall, CGI showed high correlation (r: ~90%) with other assessment instruments and it has also shown positive significant relationships and concurrent validity with other clinician's rating. In addition, the scale has good sensitivity to change over time.[81-83]

CGI-S is a 7-point (1-7) scale (1=normal, not at all ill; 7=among the most extremely ill patients) and is assessed for both Agitation and Overall Clinical Status at Screening (Day -28 to Day -1), Baseline (Day 1), Day 36 (Visit 4), Day 43 (Visit 5), and Day 70 (Visit 7).

6.2.2 Neuropsychiatric Inventory (NPI)

The NPI (Appendix 3) is a validated clinical instrument for evaluating psychopathology in a variety of disease settings, including dementia. The NPI is a retrospective caregiver-informant interview covering 12 neuropsychiatric symptom domains; delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviors, nighttime behavioral disturbances, and appetite/eating disturbances. The scripted NPI interview includes a compound screening

question for each symptom domain, followed by a list of interrogatives about domain-specific behaviors that is administered when a positive response to a screening question is elicited. Neuropsychiatric manifestations within a domain are collectively rated by the caregiver in terms of both frequency (0 to 4) and severity (1 to 3), yielding a composite symptom domain score (frequency x severity). Frequency and severity rating scales have defined anchor points to enhance the reliability of caregiver responses. Caregiver distress is rated for each positive neuropsychiatric symptom domain on a scale anchored by scores of 0 (not distressing at all) to 5 (extremely distressing). The NPI is administered to the patient's caregiver at Baseline (Day 1), Day 8 (Visit 2), Day 22 (Visit 3), Day 36 (Visit 4), Day 43 (Visit 5), Day 57 (Visit 6), and Day 70 (Visit 7)..

The NPI domains are evaluated for behaviors within the past 4 weeks. However, it also depends on the visit intervals from Baseline. The longest or maximum interval is within the past 4 weeks, as the NPI was validated based on this interval.

Therefore, for Visit 2 and 3 the evaluation will be within the past 1 and 3 weeks, respectively, and Visits 4-7 will evaluate within the past 4 weeks.

The NPI nursing home version (NPI-NH) will be used for patients from in-patient or assisted living facilities. The questions in the NPI-NH were rephrased for professional caregivers who may not know the patients prior to the onset of illness; however, the overall instrument domains and scoring is identical to the NPI.

The Agitation/Aggression domain in the NPI will be assessed as part of the total NPI as described above and the composite score obtained for this category will be recorded separately at Baseline (Day 1), Day 8 (Visit 2), Day 22 (Visit 3), Day 36 (Visit 4), Day 43 (Visit 5), Day 57 (Visit 6), and Day 70 (Visit 7).

6.2.3 Mini-Mental State Examination (MMSE)

The MMSE (Appendix 4) is a brief 30-point questionnaire test that is used to screen for cognitive impairment. It is commonly used in medicine to screen for dementia. It is also used to estimate the severity of cognitive impairment at a specific time and to follow the course of cognitive changes in an individual over time, thus making it an effective way to document an individual's response to treatment. The MMSE scale comprises 11 questions or simple tasks concerning orientation, memory, attention, and language to evaluate the patient's cognitive state.[84] It requires only 5 to 10 minutes for a trained rater to administer it. The MMSE is assessed at Screening (Day -28 to Day -1), Day 36 (Visit 4), and Day 70 (Visit 7).

6.2.4 Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (ADCS-ADL)

The ADCS-ADL inventory (Appendix 5) measures basic activities of daily living such as dressing, eating, bathing, and traveling. The 19-item version, covering mainly basic ADL, is used for the assessment of patients with more severe AD. Ratings take about 20 minutes and are based

on information obtained from the caregiver. ADCS-ADL uses a scale from 0 to 54, with lower scores indicating declining ability. The ADCS-ADL is assessed at Baseline (Day 1), Day 36 (Visit 4), and Day 70 (Visit 7).

6.2.5 The Cornell Scale for Depression in Dementia (CSDD)

The CSDD (Appendix 6) was specifically developed to assess signs and symptoms of major depression in patients with dementia.[85] Because some of these patients may give unreliable reports, the CSDD uses a comprehensive interviewing approach that derives information from the patient and the caregiver. Information is elicited through two semi-structured interviews; an interview with a caregiver and an interview with the patient. The interviews focus on depressive symptoms and signs occurring during the week preceding the assessment. The CSDD takes approximately 20 minutes to administer.

Each item is rated for severity on a scale of 0-2 (0=absent, 1=mild or intermittent, 2=severe). The item scores are added. Scores above 10 indicate a probable major depression. Scores above 18 indicate a definite major depression. Scores below 6 as a rule are associated with absence of significant depressive symptoms.

The CSDD is assessed at Screening (Day -28 to Day -1), Day 36 (Visit 4), and Day 70 (Visit 7).

6.2.6 Caregiver Strain Index (CSI)

The CSI (Appendix 7) is a tool that can be used to quickly identify families with potential caregiving concerns.[86] It is a 13-question tool that measures strain related to care provision. There is at least one item for each of the following major domains: Employment, Financial, Physical, Social, and Time. Positive responses to seven or more items on the index indicate a greater level of strain. The CSI is assessed at Baseline (Day 1), Day 8 (Visit 2), Day 22 (Visit 3), Day 36 (Visit 4), Day 43 (Visit 5), Day 57 (Visit 6), and Day 70 (Visit 7).

6.2.7 Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-cog)

The ADAS (Appendix 8) was designed to evaluate the cognitive and non-cognitive behavioral dysfunction characteristics of patients with AD.[87] The cognitive sub-scale (ADAS-cog) consists of 11 subsets related to memory, praxis, and language. The ADAS-cog takes about 30 to 45 minutes to complete.

The ADAS-cog is assessed at Baseline (Day 1), Day 36 (Visit 4), and Day 70 (Visit 7).

6.2.8 Patient Global Impression of Change (PGI-C)

The PGI-C (Appendix 9) is a 7-point (1-7) scale used to assess treatment response, and it is rated as: very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse.[80]

In this study, PGI-C will be assessed and rated by the patient's caregiver at Day 36 (Visit 4) and Day 70 (Visit 7) and will focus on the patient's agitation.

6.2.9 Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change Rating (ADCS-CGIC)

The intent of the ADCS version of the Clinical Global CGIC (Appendix 10) is to provide a means to reliably assess global change from baseline in a clinical trial. It provides a semi-structured format to allow clinicians to gather necessary clinical information from both the patient and caregiver, in order to make a global impression of clinical change. ADCS-CGIC is rated as: marked improvement, moderate improvement, minimal improvement, no change, minimal worsening, moderate worsening, or marked worsening.

The standard ADCS-CGIC instrument was modified to better assess aspects relevant to studying agitation in AD. The modified version contains additional questions related to agitation and an additional assessment of the Clinician's Impression of Change focused specifically on agitation. This modified version of the ADCS-CGIC was originally designed for the Citalopram study for Agitation in Alzheimer's disease (CitAD) and is used with permission from the study group.[88,89]

In this study, the modified ADCS-CGIC evaluation will be conducted at Baseline (Day 1) and then the modified ADCS-CGIC will be assessed at Day 36 (Visit 4) and Day 70 (Visit 7) for both Agitation and Overall Clinical Status. At Day 36 (Visit 4), the ADCS-CGIC will be completed to assess change from the Baseline (Day 1) visit. At Day 70 (Visit 7), the ADCS-CGIC will be completed to assess change from Day 36 (Visit 4) and change from the Baseline (Day 1) visit.

The ADCS-CGIC from Day 36 (Visit 4) to Day 70 (Visit 7) will be performed retrospectively for all patients who completed Visit 7 prior to Amendment 3 based on the existing ADCS-CGIC evaluation worksheets that allow the clinician to record assessments of clinical severity and of change over time.

6.2.10 Quality of Life-Alzheimer's disease measure (QoL-AD)

The QoL-AD (Appendix 11) is a brief, 13-item measure designed specifically to obtain a rating of the patient's quality of life from both the patient and the caregiver. It was developed for individuals with dementia, based on patient, caregiver, and expert input, to maximize construct validity, and to ensure that the measure focuses on quality of life domains thought to be important in cognitively impaired older adults[90] It uses simple and straightforward language and responses and includes assessments of the individual's relationships with friends and family, concerns about finances, physical condition, mood, and an overall assessment of life quality. Caregivers complete the measure as a questionnaire about their patients' QoL, while patients complete it in interview format about their own QoL. The measure consists of 13 items, rated on a 4-point scale, with 1 being poor and 4 being excellent. Total scores range from 13 to 52. It generally takes caregivers about 5 minutes to complete the measure about their patients; for patients, the interview takes about 10 to 15 minutes to administer. The QoL-AD is assessed at Baseline (Day 1), Day 36 (Visit 4), and Day 70 (Visit 7).

6.3 Safety

6.3.1 Adverse Events

6.3.1.1 Definitions

An AE is any untoward medical occurrence or unintended change (including physical, psychological, or behavioral) from the time ICF is signed, including inter-current illness, which occurs during the course of a clinical trial after treatment has started, whether considered related to treatment or not. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Changes associated with normal growth and development that do not vary in frequency or magnitude from that ordinarily anticipated clinically are not AEs (e.g., onset of menstruation occurring at a physiologically appropriate time).

Clinical AEs should be described by diagnosis and not by symptoms when possible (e.g., cold, seasonal allergies, instead of "runny nose").

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than known therapeutic doses. It must be reported irrespective of outcome even if toxic effects were not observed.

AEs will be graded on a 3-point scale and reported in detail as indicated on the eCRF:

Mild: easily tolerated, causing minimal discomfort and not interfering with normal everyday activities

Moderate: sufficiently discomforting to interfere with normal everyday activities

Severe: incapacitating and/or preventing normal everyday activities

The relationship of each AE to study medication should be determined by the investigator using the following explanations:

Not related: the event is clearly related to other factors such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient

Unlikely: the event is most likely produced by other factors such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient; **and** does not follow a known response pattern to the study medication

Possible: the event follows a reasonable temporal sequence from the time of drug administration; **and/or** follows a known response pattern to the study medication; **but** could have been produced by other factors such as the

patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient

Probable: the event follows a reasonable temporal sequence from the time of drug administration; **and** follows a known response pattern to the study medication; **and** cannot be reasonably explained by other factors such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient

6.3.1.2 Serious Adverse Events

A Serious Adverse Event (SAE) is any AE occurring at any dose that results in any of the following outcomes:

1. Death
2. Life-threatening experience (one that places the patient, in the view of the initial reporter, at immediate risk of death from the AE as it occurred, i.e., it does not include an AE that, had it occurred in a more severe form, might have caused death)
3. Persistent or significant disability/incapacity (disability is a substantial disruption of a person's ability to conduct normal life functions)
4. In-patient hospitalization or prolongation of hospitalization
5. Congenital anomaly/birth defect

Important medical events that may not result in death, or be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient or require medical or surgical intervention to prevent one of the outcomes listed in the definition.

The terms "cancer" and "overdose" are not considered to be SAEs, but if a patient experiences cancer or overdose, they are still reportable as AEs.

Pregnancy is not considered to be an AE or an SAE, unless a complication occurs that meets the requirements for an AE or SAE, but must be reported on a pregnancy report form. Women who are pregnant or likely to become pregnant are excluded from this study. In the event a patient becomes pregnant during the study, study medication must be discontinued, a pregnancy report form must be completed to capture potential drug exposure during pregnancy, and the pregnancy must be reported within 24 hours of notice. Any pregnant patient must be followed until the outcome of her pregnancy is known (i.e., normal delivery, abnormal delivery, spontaneous/voluntary/therapeutic abortion). The pregnancy (i.e., the mother and the fetus) must be followed up through delivery with regard to outcome.

A pregnancy report form must also be completed in the event that a female partner of a male patient becomes pregnant within 30 days after his last dose of study medication or study completion, whichever is greater.

The term ‘severe’ is a measure of intensity; thus a severe AE is not necessarily serious. For example, nausea of several hours duration may be rated as severe, but may not be clinically serious.

6.3.1.3 Reporting

Caregivers will be queried regarding AEs at each visit after the screening visit (Baseline [Day 1], Days 8, 22, 36, 43, 57, and 70 [Visit 2-7]). The investigator will assess and record all reported AEs. Any AE newly reported after receiving the last dose of study medication and up until 30 days after receiving the last dose of study medication will be followed up until resolution (patient’s health has returned to his/her baseline status or all variables have returned to normal) or until stabilization of the event has occurred (the investigator does not expect any further improvement or worsening of the event).

A death occurring during the study, or which comes to the attention of the investigator within 4 weeks after stopping the treatment whether considered treatment-related or not, must be reported to the sponsor.

For all SAEs, including an abnormal laboratory test value, the investigator must inform Avanir’s MM by telephone no later than 24 hours after becoming aware of the event. Subsequently, the SAE must be assessed for the following details: seriousness of event, start date, stop date, intensity, frequency, relationship to test drug, action taken regarding test drug, treatment required, and outcome to date. These details must be recorded on the clinical study AE Form that is provided. This form should be transmitted by FAX and the details given by telephone to the contact numbers below.

SAE reporting by FAX or e-mail correspondence

FAX: (734) 468-0150

E-mail: an0005sae@mmsholdings.com

SAE hotline (24-hour/7 days a week)

Phone: (877) 260-2424

Such preliminary reports will be followed by detailed descriptions later, which may include copies of hospital case reports, autopsy reports, and other related documents when requested.

The Institutional Review Board (IRB) will be notified of such an event in writing as soon as is practical in compliance with federal and local regulations.

6.3.1.4 Procedures to be Followed in the Event of Abnormal Test Values

In the event of an unexplained abnormal laboratory test result found to be clinically significant by the investigator, the test should be repeated and followed up until test values have either returned to the patient's baseline (pretreatment) range and/or until an adequate explanation of the abnormality is found.

6.3.2 Physical and Neurological Examinations

Physical and neurological examinations will be performed at Screening (Day -28 to Day -1), Day 36 (Visit 4), and Day 70 (Visit 7) and include assessments of head, eyes, ears, nose, throat, lymph nodes, skin, extremities, respiratory, gastrointestinal, musculoskeletal, cardiovascular, and nervous systems. The physical and neurological examinations should be performed by the same person each time, whenever possible.

Physical and neurological examinations abnormalities determined by the investigator to be clinically significant at Screening should be recorded as medical history.

Any clinically significant changes in physical and neurological examination findings from the screening examination should be recorded as AEs.

6.3.3 Vital Signs

Vital signs, including systolic and diastolic blood pressure (BP; mm Hg), pulse (beats/minute), respiratory rate (breaths/minute) and body temperature (^{o}C) should be recorded at all visits.

6.3.4 Clinical Laboratory Tests

The following clinical laboratory assessments are to be performed at Screening (Day -28 to Day-1), Day 36 (Visit 4), and Day 70 (Visit 7):

- Blood chemistry (calcium, magnesium, phosphorus, glucose, sodium, potassium, chloride, carbon dioxide, blood urea nitrogen [BUN], serum creatinine, uric acid, albumin, total bilirubin, alkaline phosphatase, lactate dehydrogenase [LDH], aspartate aminotransferase/serum glutamic oxaloacetic transaminase [AST/SGOT], alanine aminotransferase/serum glutamic pyruvic transaminase [ALT/SGPT], creatine kinase [CK], gamma-glutamyl transferase [GGT], triglycerides, total protein, and total cholesterol)
- Hematology (red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] count, neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, platelet count, and morphology)
- Urinalysis (pH, specific gravity, protein, glucose, ketones, and blood, and microscopic appearance)

Any patients with clinically significant abnormal laboratory test results may be required by the MM to have a repeat test 1 week later or earlier, if medically indicated. Clinically significant laboratory abnormalities may be a basis for exclusion from study entry.

6.3.5 Pregnancy Tests

Urine pregnancy tests are to be performed on females of childbearing potential at Baseline (Day 1), Day 36 (Visit 4), and on Day 70 (Visit 7).

All female patients of childbearing potential should be instructed to use appropriate birth control methods for up to 4 weeks following the last dose of study medication.

6.3.6 Electrocardiograms

A resting 12-lead ECG will be performed at all visits. At Visit 4, two ECGs will be performed; one prior to study medication dosing and one 2-3 hours after dosing. ECG equipment will be provided by the central reader. ECG data will be recorded at the study center and will include general findings, heart rate (beats/minute) QRS complex and PR and QTc intervals (milliseconds). Results will be provided by the central reader to the investigators within 24 hours. ECG data will be transferred automatically from the central reader into the eCRF monthly. ECG abnormalities present at Screening will be recorded as medical history. Any changes from the ECG status at Screening that are deemed to be clinically significant by the investigator should be captured as AEs. Any clinically significant abnormal ECG should be discussed with the study MM and, if necessary be repeated within a 1-week period.

6.4 Schedule of Evaluations and Procedures

A schedule of evaluations and procedures for both Stage 1 and Stage 2 is provided in Table 2.

Table 2 Study Schedule

Procedure	Visit:	Stage 1 Screening	Baseline	Visit 2[1]	Visit 3[2]	Visit 4[2]	Stage 2	Visit 5[1]	Visit 6[2]	Visit 7[2]/ET[3]
	Study Day:	Day -28 to -1	Day 1	Day 8	Day 22	Day 36		Day 43	Day 57	Day 70
	End of Study Week:	Week -4 to -1		Week 1	Week 3	Week 5		Week 6	Week 8	Week 10
Informed consent forms signed		X								
Medical history		X								
Review of inclusion and exclusion criteria		X	X							
Randomization (Stage 1)			X							
Re-Randomization (Stage 2)							X			
Physical and neurological examination		X				X				X
Record vital signs		X	X	X	X	X		X	X	X
Clinical Global Impression of Severity of Illness (CGI-S)		X	X			X		X		X
Resting 12-lead ECG		X	X	X	X	X	X	X	X	X
Review of adverse events			X	X	X	X		X	X	X
Review previous and concomitant medication		X	X	X	X	X		X	X	X
Mini-Mental State Examination (MMSE)		X				X				X
Neuropsychiatric Inventory (NPI)			X	X	X	X		X	X	X
Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog)			X			X				X
The Cornell Scale for Depression in Dementia (CSDD)		X				X				X
Activities of Daily Living Inventory (ADCS-ADL)			X			X				X
Caregiver Strain Index (CSI)			X	X	X	X		X	X	X
Patient Global Impression of Change (PGI-C) rated by the caregiver						X				X
Baseline ADCS-CGIC Evaluation			X							
Clinical Global Impression of Change (ADCS-CGIC)						X				X
Quality of Life-AD (QoL-AD)			X			X				X
Administer first dose of study medication in clinic			X				X			
Administer last dose of study medication in clinic										X
Chemistry, hematology, and urinalysis		X					X			X
Urine dipstick for females of childbearing potential only			X				X			X
Blood sample for PK assay							X			X
Blood sample for CYP2D6 genotyping			X							
Dispense study medication			X	X	X		X	X	X	
Review and return unused study medication and diary				X	X	X		X	X	X

[1] Visit 2 and Visit 5 have a +3 days window
[2] All study visits have a ± 3 days window (except Visit 2 and Visit 5)
[3] Early Termination visit for patients who withdraw prior to study completion

6.4.1 Description of Study Procedures

At each visit throughout the study, site staff will be required to enter information into the IWRS regarding patient data and pre-defined study assessment results. Further instructions will be provided in the IWRS Site Manual.

6.4.1.1 Screening Visit (Days -28/-1)

The following procedures carried out at the Screening visit should occur within approximately 4 weeks prior to the Baseline visit (Day 1):

1. The investigator will provide the patients, authorized representative and/or their caregivers with informed consent and/or assent documents and will explain the rationale for the study, providing ample time for participants, authorized representatives, and/or caregivers to ask questions.
2. Medical history, including patient demographics, and any concomitant medications use (including OTC medications, vitamins, and supplements) will be reviewed and recorded.
3. Physical and neurological examination findings and vital signs measurements (including BP, heart rate, respiratory rate, and body temperature) will be recorded.
4. Clinical laboratory assessments:
    - Blood chemistry (calcium, phosphorus, magnesium, glucose, sodium, potassium, chloride, carbon dioxide, BUN, serum creatinine, uric acid, albumin, total bilirubin, alkaline phosphatase, LDH, AST/SGOT, ALT/SGPT, CK, GGT, triglycerides, total protein, and total cholesterol)
    - Hematology (RBC count, hemoglobin, hematocrit, WBC count, neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, platelet count, and morphology)
    - Urinalysis (pH, specific gravity, protein, glucose, ketones, and blood, and microscopic appearance)
5. A resting 12-lead ECG will be performed.
6. Review inclusion/exclusion criteria.
7. The MMSE test will be completed. A score between 8 and 28 (inclusive) is required for study entry.
8. The Clinical Global Impression of Severity of Illness (CGI-S) scale will be completed. A score ≥4 on the CGI-S assessing Agitation is required for study entry.
9. The CSDD will be completed. A score <10 is required for study entry.

Following screening procedures for assessment of inclusion and exclusion criteria, the site will complete a protocol eligibility form and submit to the MM for approval. Patients deemed eligible by the PI and the MM will be randomized into the study. Patients who have ECG or laboratory test results outside of the reference normal range that the investigator considers to be clinically significant, and may put the patient at a higher risk for study participation, will not be enrolled.

6.4.1.2 Baseline Visit (Day 1)

The Baseline (Day 1) visit should occur in the morning.

The following procedures will be performed at Baseline (Day 1):

Before Dosing:

1. The CGI-S will be completed
2. Vital signs will be measured and recorded.
3. Caregivers will be queried regarding any current concomitant medication use (including OTC, vitamins, and supplements).
4. The caregiver will be queried regarding AEs.
5. A urinary beta-human chorionic gonadotropin (beta-hCG) test will be performed (females of childbearing potential only).
6. A blood specimen will be collected for CYP2D6 genotyping.
7. The NPI will be completed.
8. The ADCS-ADL will be completed.
9. The ADAS-cog will be completed.
10. The CSI will be completed.
11. The baseline evaluation for the CGIC will be completed.
12. The Quality of Life-Alzheimer's disease (QoL-AD) measure will be completed.

Patients will be randomized once it is determined that they satisfy all of the inclusion and exclusion criteria (on the basis of the screening and baseline assessments described above) and will be assigned with a study medication kit number via IWRS.

Study Medication Dosing:

The first dose of study medication will be administered from the white label bottle at the clinic regardless of the time of day.

After Dosing:

1. A resting 12-lead ECG will be performed between 2 and 3 hours (± 15 minutes) after taking the morning dose of study medication.
2. The caregiver will be queried regarding AEs.

3. Sufficient study medication will be dispensed for a 1-week treatment period (1 kit containing two 18-count bottles).

Caregivers will be instructed to administer to the patient 1 capsule of study medication from the 18-count white label bottle in the morning and 1 capsule of study medication from the 18-count blue label bottle in the evening, approximately every 12 hours ±4 hours, for 7 days.

Patient/Caregiver Instruction

The investigator and/or clinical coordinator will give patients and caregivers detailed instructions regarding study procedures, including how to complete the Patient's Diary Card. They will also be instructed to consult with the study site prior to taking any non-study medications. These requirements will be reviewed in person, and written instructions will be provided to the patient and their caregiver. Caregivers will also be instructed to bring to the clinic any unused study medication at each study visit. Caregivers will be queried at the end of each visit to be certain they understand what is required of them.

6.4.1.3 Visit 2 (Day 8 + 3-day window)

Caregiver is advised to administer to the patient the morning dose of study medication within 2 hours prior to the clinic appointment.

The following procedures will be performed:

1. Vital signs will be measured and recorded.
2. A resting 12-lead ECG will be performed between 2 and 3 hours (± 15 minutes) after taking the morning dose of study medication.
3. The NPI will be completed.
4. The CSI will be completed.
6. The Patient's Diary Card will be collected and reviewed for compliance. A new diary card will be dispensed.
7. The caregiver will be queried regarding AEs and concomitant medication use (including OTC medications, vitamins, and supplements).
8. Returned, unused study medication will be accounted for compliance.
9. New study medication will be dispensed for a 2-week treatment period (1 kit containing two 18-count bottles). The study medication kit number will be assigned by IWRS.

Caregivers will be instructed to administer to the patient the study medication twice-daily (1 capsule from the white label bottle in the morning and 1 capsule from the blue label bottle in the evening, approximately every 12 hours ±4 hours) for 14 days.

Patient/Caregiver Instruction

The investigator and/or clinical coordinator will give patients and caregivers detailed instructions regarding study procedures including how to complete the Patient's Diary Card. They will also be instructed to consult with the study site prior to taking any non-study medications. These

requirements will be reviewed in person, and written instructions will be provided to the patient and their caregiver. Caregivers will also be instructed to bring to the clinic any unused study medication at each study visit. Caregivers will be queried at the end of each visit to be certain that they understand what is required of them.

6.4.1.4 Visit 3 (Day 22 ± 3-day window)

The caregiver will be advised to administer the morning dose of study medication to the patient within 2 hours prior to the clinic appointment.

The following procedures will be performed:

1. Vital signs will be recorded.
2. A resting 12-lead ECG will be performed between 2 and 3 hours (± 15 minutes) after taking the morning dose of study medication.
3. The NPI will be completed.
4. The CSI will be completed.
5. The Patient's Diary Card will be collected and reviewed for compliance. A new diary card will be dispensed.
6. The caregiver will be queried regarding AEs and concomitant medication use (including OTC medications, vitamins, and supplements).
7. Returned, unused study medication will be accounted for compliance.
8. New study medication will be dispensed for a 2-week treatment period (1 kit containing two 18-count bottles). The study medication kit number will be assigned by IWRS.

Caregivers will be instructed to administer to the patient the study medication twice-daily (1 capsule from the white label bottle in the morning and 1 capsule from the blue label bottle in the evening, approximately every 12 hours ±4 hours) for 14 days.

Patient/Caregiver Instruction

The investigator and/or clinical coordinator will give patients and caregivers detailed instructions regarding study procedures including how to complete the Patient's Diary Card. They will also be instructed to consult with the study site prior to taking any non-study medications. These requirements will be reviewed in person, and written instructions will be provided to the patient and their caregiver. The caregivers will also be instructed to bring to the clinic any unused study medication at each study visit. Caregivers will be queried at the end of each visit to be certain that they understand what is required of them.

6.4.1.5 Visit 4, End of Stage 1/Beginning of Stage 2 (Day 36 ± 3-day window)

Visit 4 (Day 36) should occur in the morning.

The morning dose of study medication will be taken at the clinic after the required procedures are performed.

The following procedures will be performed before dosing (End of Stage 1):

1. Physical and neurological examination will be performed.
2. Vital signs will be recorded.
3. A resting 12-lead ECG will be performed.
4. The CGI-S will be completed.
5. The MMSE will be completed.
6. The NPI will be completed.
7. The CSDD will be completed.
8. The ADAS-cog will be completed.
9. The ADCS-ADL will be completed.
10. The CSI will be completed.
11. The PGI-C will be completed.
12. The ADCS-CGIC will be completed (assess change from Baseline).
13. The QoL-AD will be completed.
14. The Patient's Diary Card will be collected and reviewed for compliance.
15. The caregiver will be queried regarding AEs and concomitant medication use (including OTC, vitamins, and supplements).
16. Returned, unused study medication will be accounted for compliance.

Beginning of Stage 2

Patients will be re-randomized after the procedures above have been completed. A new study medication kit number will be assigned via IWRS. The patient number will remain the same.

Study Medication Dosing:

One capsule of study medication from the newly dispensed white label bottle will be administered to the patient at the clinic regardless of the time of day.

After Dosing:

1. A blood specimen will be collected within 3 hours after the morning dose of study medication has been taken for analysis of plasma DM, DX, and Q levels and the clinical laboratory assessments listed below:
    - Blood chemistry (calcium, phosphorus, magnesium, glucose, sodium, potassium, chloride, carbon dioxide, BUN, serum creatinine, uric acid, albumin, total bilirubin, alkaline phosphatase, LDH, AST/SGOT, ALT/SGPT, CK, GGT, triglycerides, total protein, and total cholesterol)

- Hematology (RBC count, hemoglobin, hematocrit, WBC count, neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, platelet count, and morphology)
- Urine will be collected for urinalysis (pH, specific gravity, protein, glucose, ketones, and blood, and microscopic appearance)
- Urinary pregnancy test will be performed in women of childbearing potential.
- The time of drug administration and collection of the specimens should be recorded.

2. A resting 12-lead ECG will be performed between 2 and 3 hours (± 15 minutes) after taking the morning dose of study medication.
3. A new Patient's Diary Card will be dispensed.
4. Sufficient study medication will be dispensed for a 1-week treatment period (1 kit containing two 18-count bottles).

Caregivers will be instructed to administer to the patient the study medication twice-daily (1 capsule from the white label bottle in the morning and 1 capsule from the blue label bottle in the evening, approximately every 12 hours ±4 hours) for 7 days.

Patient/Caregiver Instruction

The investigator and/or clinical coordinator will give patients and caregivers detailed instructions regarding study procedures including how to complete the Patient's Diary Card. They will also be instructed to consult with the study site prior to taking any non-study medications. These requirements will be reviewed in person, and written instructions will be provided to the patient and their caregiver. Caregivers will also be instructed to bring to the clinic any unused study medication at each study visit. Caregivers will be queried at the end of each visit to be certain that they understand what is required of them.

6.4.1.6 Visit 5 (Day 43 + 3-day window)

The caregiver will be advised to administer to the patient the morning dose of study medication within 2 hours prior to the clinic appointment.

The following procedures will be performed:

1. Vital signs will be recorded.
2. A resting 12-lead ECG will be performed between 2 and 3 hours (± 15 minutes) after taking the morning dose of study medication.
3. The NPI will be completed.
4. The CGI-S will be completed.
5. The CSI will be completed.
6. The Patient's Diary Card will be collected and reviewed for compliance. A new diary card will be dispensed.

7. The caregiver will be queried regarding AEs and concomitant medication use (including OTC medications, vitamins, and supplements).
8. Returned, unused study medication will be accounted for compliance.
9. Study medication will be dispensed for a 2-week treatment period (1 kit containing two 18-count bottles). The study medication kit number will be assigned by IWRS.

Caregivers will be instructed to administer to the patient the study medication twice-daily (1 capsule from the white label bottle in the morning and 1 capsule from the blue label bottle in the evening, approximately every 12 hours ±4 hours) for 14 days.

Patient/Caregiver Instruction

The investigator and/or clinical coordinator will give patients and caregivers detailed instructions regarding study procedures including how to complete the Patient's Diary Card. They will also be instructed to consult with the study site prior to taking any non-study medications. These requirements will be reviewed in person, and written instructions will be provided to the patient and their caregiver. The caregivers will also be instructed to bring to the clinic any unused study medication at each study visit. Caregivers will be queried at the end of each visit to be certain that they understand what is required of them.

6.4.1.7 Visit 6 (Day 57 ± 3-day window)

The caregiver will be advised to administer to the patient the morning dose of study medication within 2 hours prior to the clinic appointment.

The following procedures will be performed:

1. Vital signs will be recorded.
2. A resting 12-lead ECG will be performed between 2 and 3 hours (± 15 minutes) after taking the morning dose of study medication.
3. The NPI will be completed.
4. The CSI will be completed.
5. The Patient's Diary Card will be collected and reviewed for compliance. A new diary card will be dispensed.
6. The caregiver will be queried regarding AEs and concomitant medication use (including OTC medications, vitamins, and supplements).
7. Returned, unused study medication will be accounted for compliance.
8. Study medication will be dispensed for a 2-week treatment period (1 kit containing two 18-count bottles). The study medication kit number will be assigned by IWRS.

Caregivers will be instructed to administer to the patient the study medication twice-daily (1 capsule from the white label bottle in the morning and 1 capsule from the blue label bottle in the evening, approximately every 12 hours ±4 hours) for 14 days.

Patient/Caregiver Instruction

The investigator and/or clinical coordinator will give patients and caregivers detailed instructions regarding study procedures including how to complete the Patient's Diary Card. They will also be instructed to consult with the study site prior to taking any non-study medications. These requirements will be reviewed in person, and written instructions will be provided to the patient and their caregiver. The caregivers will also be instructed to bring to the clinic any unused study medication at each study visit. Caregivers will be queried at the end of each visit to be certain that they understand what is required of them.

6.4.1.8 Visit 7 (Day 70 ± 3-day window) / Early Termination

Visit 7 (Day 70) should occur in the morning. Patients who withdraw prior to study completion are required to complete study procedures as listed in Visit 7 within 48 hours of the last dose of study medication. There is no specific time frame for the 12-lead ECG, safety labs and PK samples for early termination patients.

The last dose of study medication will be administered to the patient from the white label bottle at the clinic regardless of the time of day.

The following procedures will be performed:

1. Physical neurological examination will be performed.
2. Vital signs will be recorded.
3. A resting 12-lead ECG will be performed between 2 and 3 hours (± 15 minutes) after taking the morning dose of study medication.
4. The MMSE will be completed.
5. The NPI will be completed.
6. The CGI-S will be completed.
7. The CSDD will be completed.
8. The ADAS-cog will be completed.
9. The ADCS-ADL will be completed.
10. The CSI will be completed.
11. The PGI-C will be completed.
12. The ADCS-CGIC will be completed (assess change from Visit 4 and change from Baseline).
13. The QoL-AD will be completed.
14. The Patient's Diary Card will be collected and reviewed. Study medication administration information will be reviewed for compliance.
15. A blood specimen will be collected within 3 hours after the morning dose of study medication has been taken for analysis of plasma DM, DX, and Q levels. The time of drug administration and specimen collection should be recorded.

16. Clinical laboratory assessments:
    - Blood chemistry (calcium, phosphorus, magnesium, glucose, sodium, potassium, chloride, carbon dioxide, BUN, serum creatinine, uric acid, albumin, total bilirubin, alkaline phosphatase, LDH, AST/SGOT, ALT/SGPT, CK, GGT, triglycerides, total protein, and total cholesterol)
    - Hematology (RBC count, hemoglobin, hematocrit, WBC count, neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, platelet count, and morphology)
    - Urinalysis (pH, specific gravity, protein, glucose, ketones, and blood, and microscopic appearance)
    - Urinary pregnancy test will be performed in women of childbearing potential.
17. The caregiver will be queried regarding AEs and concomitant medication use (including OTC, vitamins, and supplements).
18. Returned, unused study medication will be accounted for compliance.

Any AE previously reported and not yet resolved at the time of this visit, will be followed-up until resolution (patient's health has returned to his/her baseline status or all variables have returned to normal) or until stabilization of the event has occurred (the investigator does not expect any further improvement or worsening of the event).

Any newly reported AE after receiving and up to 30 days after the last dose of study medication will be followed up until resolution (patient's health has returned to his/her baseline status or all variables have returned to normal) or until stabilization of the event has occurred (the investigator does not expect any further improvement or worsening of the event).

7 Data Management

7.1 Data Collection

Data collected during the study will be recorded in the patient's eCRF by trained investigational center staff. The staff will keep records of the patient's visit in the files considered as source documents for that center, e.g., hospital chart, research chart, study assessments, and questionnaires, etc. To ensure that data have been entered correctly on the eCRF, the eCRFs will be 100% source-data verified by a monitor from the sponsor/representative, who will notify the investigator regarding questions or missing data. The investigator or authorized designee will be responsible for the timely recording of patient data. It is recommended that source document information be entered into the eCRF within 5 business days of a patient's study visit.

The investigator or authorized designee will review all eCRFs (including the termination page after the patient's final visit) for completeness and accuracy and will electronically sign the eCRFs attesting to this when directed by the contract research organization (CRO) in a timely manner. Non-eCRF data including, but not limited to, laboratory tests and ECG results, will be sent to the CRO by data transfer from the appropriate vendor for assimilation into the database.

The sponsor or representative will create and provide access to the eCRF to authorized site personnel. All eCRF information is to be completed. If an item is not available or is not applicable, this fact should be indicated in the source document as well as any applicable comments fields. Blank fields should not be present unless otherwise directed. Each completed eCRF must be reviewed, signed, and dated by the investigator as outlined in the project timeline. The completed eCRF will be reviewed by data management after monitoring is complete. A copy of the completed eCRF will be provided to the investigator. The copy (e.g., compact disc read-only-memory [CD-ROM]) will remain at the site in the investigator's files. All data collected in this study will be integrated into an appropriate preformatted database and submitted to the sponsor or designee for statistical evaluation. Data validation and edit checks will be conducted on the data. Any discrepancies will be noted and queries will be generated by the sponsor's designee to be resolved by the center. Queries should be resolved by the investigational center in a timely manner.

A quality assurance audit will be performed. When all issues from the audit are resolved, and all data management processes are completed for finalizing the database, the database will be locked and ready for analysis.

The investigator and clinical center must permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to source data/documents.

8 Statistical Methods

8.1 Analysis Populations

Modified Intent-to-Treat (MITT) Population: The MITT population is defined as follows:

- All patients randomized in Stage 1 who had at least one post-Baseline efficacy assessment in Stage 1
- All placebo non-responders from Stage 1 who are re-randomized and had at least one post-week 5 efficacy assessment in Stage 2

The MITT population will be used for all analyses of efficacy. Patients will be included in the treatment group to which they were randomized, regardless of treatment received.

Intent-to-Treat (ITT) Population: The ITT population includes all randomized patients in Stage 1 and Stage 2. The ITT population will be used for exploratory efficacy analyses.

Safety Population: The safety population includes all patients who received study treatment. The safety population will be used for all analyses of safety and patients will be included in the treatment group based on treatment received.

8.2 Demographic and Baseline Characteristics

Baseline characteristics, such as demographics, will be summarized by treatment group for the ITT and MITT populations.

8.3 Efficacy Analysis

8.3.1 Study Endpoints

Efficacy Endpoints:

As AVP-923 has not been specifically studied for treating behavioral disturbances in patients with dementia, preliminary data from which to base an assessment of the endpoint(s) that are most likely to demonstrate a beneficial effect of treatment (e.g. agitation) are not available. However, the Agitation/Aggression domain of the Neuropsychiatric Inventory (NPI) is pre-specified as the primary endpoint. It may be the case that one of the secondary endpoints (see below) may be a more appropriate endpoint for future studies.

The primary and secondary efficacy endpoints are assessed in each of the two stages of the trial. For the primary efficacy analysis, as well as for all other efficacy analyses in which the data from the two stages are combined, the endpoint definition is based on both the change from Baseline to week 5 and on the change from the week 5 to week 10. Similarly, the analyses of the two stages combined at other time points are based on combining the data from, for example, weeks 1 and 6, and weeks 3 and 8.

Primary:

The primary efficacy endpoint is the change from baseline to week 5 and week 10 in the Agitation/Aggression domain of the NPI.

Secondary:

Change from baseline to week 5 and week 10 in the total NPI

Change from baseline to week 5 and week 10 in the ADCS-ADL

PGI-C (rated by a caregiver) at week 5 and week 10

ADCS-CGIC at week 5 and week 10

Change from baseline to week 1 and week 6 in the Agitation/Aggression domain in the NPI

Change from baseline to week 3 and week 8 in the Agitation/Aggression domain in the NPI

Change from baseline to week 5 and week 10 in the QoL-AD

Change from baseline to week 5 and week 10 in the CSDD

Change from baseline to week 5 and week 10 in the CSI

Changes in concomitant use of psychotropic drugs

Exploratory:

Change from baseline to week 5 and week 10 in the ADAS-cog

8.3.2 Primary Efficacy Analysis

The primary efficacy analysis will be carried out using the weighted least squares model for a two-stage design described by Chen et al. [91] The AVP-923 and placebo groups will be compared using a two-sided test at the alpha=0.05 level of significance.

8.3.3 Secondary Efficacy Analyses

Secondary endpoints will be analyzed using the same methodology as described for the primary efficacy analysis. In addition, for each stage separately, the Cochran-Mantel-Haenszel mean score test (using equally spaced scores) will be used to compare the AVP-923 and placebo groups. All secondary analyses will be completed using two-sided tests at the alpha=0.05 level of significance.

8.3.4 Exploratory Efficacy Analyses

Exploratory analysis of cognitive function will be assessed using ADAS-cog. Additional efficacy analyses will be carried out using the ITT population. The primary objectives of these analyses will be to characterize the longer-term efficacy (from Stages 1 and 2) in patients randomized to AVP-923 in Stage 1 and to investigate the efficacy of AVP-923 in placebo responders from

Stage 1. The analyses will also explore potential effects from protocol specified dose escalations. These analyses will be described in the Statistical Analysis Plan (SAP).

The statistical analyses, including exploratory endpoints, are described in more detail in the SAP.

8.3.5 CYP2D6 Genotype

Genotype information will be used to classify patients as either poor metabolizers of DM or extensive metabolizers of DM. Patients who are intermediate metabolizers will be included with the poor metabolizers; ultra-rapid metabolizers will be included with the extensive metabolizers for analysis.

8.4 Safety

Safety will be assessed by the following measurements:

- AEs
- Physical and neurological examination
- Vital signs (including BP, heart rate, respiratory rate, and body temperature)
- Clinical laboratory values such as serum biochemistry, hematology, and urinalysis
- Resting 12-lead ECG

Safety analyses will consist of data summaries for biological parameters and AEs. Safety analyses will be tabulated by treatment.

8.4.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The percentages of patients experiencing one or more AEs will be summarized by treatment, system organ class (SOC), deaths, nonfatal SAEs, AEs, AEs resulting in study discontinuation, and treatment-emergent AEs (TEAE). TEAEs are those AEs that occur after the first dose of study medication up until 30 days after last dose. Physical and Neurological Examination

Changes in abnormalities from baseline and at the end of treatment will be compared between treatments.

8.4.2 Vital Signs and ECGs

Summary statistics of absolute values and percentage change from baseline for BP (diastolic and systolic) and heart rate, respiratory rate, and ECG parameters will be provided. All values outside a pre-defined normal range will be highlighted in the individual patient data listings.

8.4.3 Clinical Laboratory Values

Laboratory parameters will be summarized via descriptive statistics and via shifts in results in respect to normal ranges between baseline and end of treatment as increased, decreased, or no change.

8.4.4 Data and Safety Monitoring Board

The sponsor will appoint a Data and Safety Monitoring Board (DSMB) for the periodic review of available study data.

The DSMB is an independent group of experts that advises the sponsor and the study investigators. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DSMB are to (1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and (2) make recommendations to the sponsor concerning the continuation, modification, or termination of the trial.

The DSMB considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study.

The DSMB is responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review, stopping guidelines, unmasking (unblinding), and voting procedures prior to initiating any data review. The DSMB is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

8.4.5 Interim Analysis

Interim safety analyses will be conducted as per the DSMB charter. All necessary safeguards as described in the charter will be put in place to avoid unblinding of study staff or introduction of bias.

An interim analysis of efficacy may be carried out. If so, the protocol will be amended to provide details.

8.5 PK Analysis

PK results (DM, DX, and Q concentration data) will be summarized descriptively overall and by metabolizer group.

8.6 Sample Size Calculations

Based on the analysis of published results of previously conducted clinical studies,[35-39] estimates of the standard deviation (SD) of the change from baseline in the NPI Agitation/Aggression score range from 3.1 to 5.2 points. Assuming an SD of 5.0 points, and based on the use of a two-sided, two-sample comparison of means from independent samples at the 5% level of significance, a

total sample size of 196 patients (randomized in a 3:4 [AVP-923:placebo] ratio) will provide greater than 90% power to detect a mean difference of 2.5 points. However, the magnitude of the true treatment difference is unknown. If the treatment difference is 2.0 points, then the power to detect such a difference will be less than 75%. In addition, if the SD of the change from baseline in the NPI Agitation/Aggression score is larger than in prior studies, the power will be further reduced. As a result, this study should be considered to be an exploratory trial, the results of which will be used to design subsequent studies.

9 Administrative Procedures

9.1 Institutional Review Board Approval

Institutional Review Boards must meet the guidelines set out by the FDA and conform to local laws and customs where appropriate. Written IRB approval for the protocol and the signed ICF must be obtained and transmitted to Avanir Pharmaceuticals or representative before the study can be initiated. The IRB must be informed of and approve all protocol amendments. The investigator will ensure that this study is conducted in full conformance with the laws and regulations of the US (see, Appendix 12 Investigator Responsibilities). The complete text of the World Medical Association Declaration of Helsinki is given in Appendix 13.

9.2 Informed Consent Form

The ICF will follow the principles outlined in the current version of the Declaration of Helsinki. For each patient found to be eligible for the study, informed consent will be obtained from the patient (if the patient is capable in the judgment of the investigator to provide informed consent) or the authorized representative. For patients that are not capable of providing informed consent, but are capable of providing assent, the patient will be asked to provide assent. If the patient is not capable of providing assent, the investigator will document the reasons why and maintain that documentation with the other informed consent documents. The patient's caregiver will also be asked to provide informed consent as they will be providing data on themselves and the patient, as well as, being responsible for ensuring compliance from the patient between study visits.

The patients and/or patient's authorized representative and the caregiver will be properly informed of the purpose of the study. The patients and/or patient's authorized representative and the caregiver will be alerted to any anticipated AE that may be encountered with the study medication. A signed ICF will be obtained from all patients and/or patient's authorized representative and the caregiver prior to patient entry into this study. Patients and/or patient's authorized representative and the caregiver will be provided with a copy of their signed ICF.

9.3 Patient's Diary Card

The Patient's Diary Card will be reviewed by clinical study personnel at all study treatment visits for confirmation of medication dosage and any rescue medication received. The study personnel are responsible for (i) ensuring that patients and/or caregivers are properly collecting data and recording it into the diaries; and (ii) transcribing the diary recordings into the eCRF. The diary will be collected at all study visits after baseline. The originals of all diaries will be maintained at the site as source documents.

9.4 Electronic Case Report Forms

For each patient enrolled who has given informed consent, an eCRF must be completed and electronically signed by the investigator to certify that the data within each eCRF are complete and correct. This also applies to those patients who fail to complete the study. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to document the outcome.

Any site personnel delegated responsibility for data entry, query resolution, or eCRF approval must complete training prior to accessing the eCRF. The electronic data capture (EDC) vendor will provide a username once training completion has been confirmed and the account has been approved by the sponsor. Changes to the data once it has been initially saved will be tracked via audit trail and will require a reason for the change. The audit trail will also include who made the change and a date/time stamp.

The eCRFs will be reviewed by the study monitor at the study site. Errors detected by subsequent in-house data review may necessitate clarification or correction of errors. All changes will be documented and approved by the investigator.

All investigators will be provided with copies of the eCRFs for their site on a CD-ROM at the end of the study.

9.5 Quality Assurance

9.5.1 Documentation

For each process, evaluation, or test that generates study data but is not described in the protocol or eCRF, a written description of the data generation procedures shall be retained in the quality assurance section of the study files. In the case of routine clinical diagnostic procedures, only a copy of the relevant certification document is required.

9.5.2 Monitoring

Throughout the course of the study, the study monitor will make frequent contacts with the investigator. This will include telephone calls and on-site visits. The study will be routinely monitored to ensure compliance with the study protocol and the overall quality of data collected. During the on-site visits, the eCRFs will be reviewed for completeness and adherence to the protocol. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor may periodically request review of the investigator study file to assure the completeness of documentation in all respects of clinical study conduct.

The study monitor will verify that each patient has proper consent documentation from the patient and/or patient’s authorized representative and the caregiver for study procedures and for the release of medical records to the sponsor, FDA, other regulatory authorities, and the IRB. The study monitor will also verify that assent was obtained for patients not capable of providing informed consent or that documentation is provided by the investigator explaining why the

patient was unable to provide assent. The investigator or appointed delegate will receive the study monitor during these on-site visits and will cooperate in providing the documents for inspection and respond to inquiries. In addition, the investigator will permit inspection of the study files by authorized representatives of the regulatory agencies.

On completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

9.6 Record Retention

To enable evaluations and/or audits from regulatory authorities or Avanir, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Trial Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Avanir should be prospectively notified. The study records must be transferred to a designee acceptable by Avanir, such as another investigator, another institution, or to Avanir. The investigator must obtain Avanir's written permission before disposing of any records, even if retention requirements have been met.

9.7 Source Data

The documents that will form the source data for the clinical study (e.g., patient charts, laboratory reports) must be defined and documented in the in-house study master file prior to the start of the study. Data on the eCRFs which will be checked against source data during monitoring visits must also be defined and documented in the in-house study master file including the percentage of each of the source data to be verified and the percentage of patients' eCRFs to be monitored.

9.8 Data Handling

Data collected on the eCRFs will be entered into EDC system by trained site staff. Any queries arising from data entry will be checked with the investigator and changes approved.

9.9 Laboratory Procedures

Each individual site laboratory will collect hematology and chemistry blood samples for analysis. Instructions for specimen evaluation and transport to a central laboratory will be provided at the time of study initiation. Blood samples will also be taken for CYP2D6 genotyping at Baseline (Day 1) and for determination of DM, DX, and Q in plasma on Visits 4 and 7 (Day 36 and

Day 70). Instructions for shipping the laboratory samples for evaluation by central facilities will be provided.

9.10 Guidelines for Good Clinical Practice

Standards for GCP must be adhered to for all study-based procedures.

9.11 Conditions for Amending the Protocol

Protocol modification to ongoing studies which could potentially adversely affect the safety of patients or which alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, duration of therapy, assessment variables, the number of patients treated, or patient selection criteria must be made only after appropriate consultation between an appropriate representative of Avanir and the investigator.

Protocol modifications must be prepared by a representative of Avanir or the investigator, and reviewed and approved by Avanir. All major changes must be addressed and when appropriate, justified in the Background and/or Study Design section of the protocol.

All protocol modifications must be reviewed and approved by the appropriate IRB in accordance with local requirements, before the revised edition can be implemented. Modifications which eliminate an apparent immediate hazard to patients do not require pre-approval by the IRB.

9.12 Conditions for Terminating the Study

Both Avanir and the principal investigator reserve the right to terminate the study at the site at any time. Should this be necessary, the procedures to effect study termination will be arranged after review and consultation by both parties. In terminating the study, Avanir and the investigator will assure that adequate consideration is given to the protection of the patient's interests.

9.13 Confidentiality of Study Documents and Patient Records

The investigator must assure that the patient's anonymity will be maintained. On eCRFs or other documents submitted to Avanir, patients should not be identified by their names but by an identification code.

The investigator should keep a separate log of patient's codes, names, and addresses. Documents not for submission to Avanir, for example, patients' signed ICFs, should be maintained by the investigator in strict confidence.

9.14 Reports

At the completion of the study, the investigator shall provide the sponsor with an adequate report shortly after completion of the investigator's participation in the study as described in the Code of Federal Regulations (CFR) Title 21, Part 312.64.

9.15 Publications

It is anticipated that a report of this study will be published in the scientific literature by the sponsor. The investigator will not seek to arrange for publication of any of the information or results from the study in any scientific journal, or other publication or by way of lecture without Avanir's prior review and written consent.

9.16 Audits/Inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel or designee(s) from Avanir or to health authority inspectors after appropriate notification. The verification of the eCRF data may be by direct inspection of source documents (where permitted by law) or through an interview exchange.

The inspector from the regulatory authority will be especially interested in the following items:

- Visits from the sponsor's representatives
- IRB approval(s)
- Study medication accountability
- Study protocol and amendments
- ICFs of the patient (if capable of providing ICF, according to the investigator) or patient's authorized representatives and caregivers
- Assent of the patients (if capable of providing assent, according to the investigator)
- Medical records supportive of eCRF data
- Reports to the IRB and the sponsor
- Record retention

The sponsor will be available to help investigators prepare for an inspection.

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11 Appendices

Appendix 1: AVP-923-20 (Nuedexta™) Full Prescribing Information

The link to Daily Med web site is the most recent drug labeling submitted to the Food and Drug Administration (FDA):

http://dailymed.nlm.nih.gov/dailymed/about.cfm

Appendix 2: Clinical Global Impression of Severity of Illness (CGI-S) Sample

MODIFIED CLINICAL GLOBAL IMPRESSION OF SEVERITY WORKSHEET (CGI-S)

Screening, Baseline, and Visits 4, 5, and 7

SITE NUMBER	PATIENT NUMBER	PATIENT INITIALS	VISIT NUMBER	VISIT DATE	EXAMINER INITIALS

Severity of Illness:

Considering your total experience with this particular population, what is the Patient's Overall Clinical Status at this time?

- ☐ 0 = Not assessed
- ☐ 1 = Normal, not at all ill
- ☐ 2 = Borderline ill
- ☐ 3 = Mildly ill
- ☐ 4 = Moderately ill
- ☐ 5 = Markedly ill
- ☐ 6 = Severely ill
- ☐ 7 = Among the most extremely ill patient

Severity of Agitation:

Considering your total experience with this particular population, what is the status of the Patient's Agitation Syndrome?

- ☐ 0 = Not assessed
- ☐ 1 = Normal, not at all ill
- ☐ 2 = Borderline ill
- ☐ 3 = Mildly ill
- ☐ 4 = Moderately ill
- ☐ 5 = Markedly ill
- ☐ 6 = Severely ill
- ☐ 7 = Among the most extremely ill patient

Reference: Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

Appendix 3: Neuropsychiatric Inventory (NPI) Sample

NEUROPSYCHIATRIC INVENTORY (NPI)

Baseline and Visits 2 through 7

SITE NUMBER	PATIENT NUMBER	PATIENT INITIALS	VISIT NUMBER	VISIT DATE	EXAMINER INITIALS

A. DELUSIONS (NA)

Does the patient have beliefs that you know are not true? For example, saying that people are trying to harm him/her or steal from him/her. Has he/she said that family members are not who they say they are or that the house is not their home? I'm not asking about mere suspiciousness; I am interested if the patient is convinced that these things are happening to him/her?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐ N/A

1.	Does the patient believe that he/she is in danger – that others are planning to hurt him/her?	☐ Yes	☐ No
2.	Does the patient believe that others are stealing from him/her?	☐ Yes	☐ No
3.	Does the patient believe that his/her spouse is having an affair?	☐ Yes	☐ No
4.	Does the patient believe that unwelcome guests are living in his/her house?	☐ Yes	☐ No
5.	Does the patient believe that his/her spouse or others are not who they claim to be?	☐ Yes	☐ No
6.	Does the patient believe that his/her house is not his/her home?	☐ Yes	☐ No
7.	Does the patient believe that family members plan to abandon him/her?	☐ Yes	☐ No
8.	Does the patient believe that television or magazine figures are actually present in the room? (Does he/she try to talk or interact with them?)	☐ Yes	☐ No
9.	Does the patient believe any other unusual things that I haven't asked about?	☐ Yes	☐ No

Comments: _____

_____

If the screening question is confirmed, determine the frequency and severity of the delusions (based on the most frequent symptom).

Frequency:

☐ 1. Occasionally – less than once per week
☐ 2. Often – about once per week
☐ 3. Frequently– several times per week but less than every day
☐ 4. Very frequently – once or more per day

Severity:

☐ 1. Mild – delusions present but seem harmless and produce little distress in the patient
☐ 2. Moderate – delusions are distressing and disruptive.
☐ 3. Marked – delusions are very disruptive and are a major source of behavioral disruption [If PRN medications are prescribed, their use signals that the delusions are of marked severity]

Distress: How emotionally distressing do you find this behavior?

☐ 0. Not at all
☐ 1. Minimally
☐ 2. Mildly
☐ 3. Moderately
☐ 4. Severely
☐ 5. Very severely or extremely

NEUROPSYCHIATRIC INVENTORY (NPI)

Baseline and Visits 2 through 7

B. Hallucinations (NA)

Does the patient have hallucinations such as seeing false visions or hearing imaginary voices? Does he/she seem to see, hear or experience things that are not present? By this question we do not mean just mistaken beliefs such as stating that someone who has died is still alive, rather we are asking if the patient actually has abnormal experiences of sounds or visions.

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐ N/A

1.	Does the patient describe hearing voices or act as if he/she hears voices?	☐ Yes	☐ No
2.	Does the patient talk to people who are not there?	☐ Yes	☐ No
3.	Does the patient describe seeing things not seen by others or behave as if he/she is seeing things not seen by others (people, animal, lights, etc)?	☐ Yes	☐ No
4.	Does the patient report smelling odors not smelled by others?	☐ Yes	☐ No
5.	Does the patient describe feeling things on his/her skin or otherwise appear to be feeling things crawling or touching him/her?	☐ Yes	☐ No
6.	Does the patient describe tastes that are without any known cause?	☐ Yes	☐ No
7.	Does the patient describe any other unusual sensory experiences?	☐ Yes	☐ No

Comments: _____

_____

If the screening question is confirmed, determine the frequency and severity of the hallucinations (based on the most frequent symptom).

Frequency:

☐ 1. Occasionally – less than once per week
☐ 2. Often – about once per week
☐ 3. Frequently– several times per week but less than every day
☐ 4. Very frequently – once or more per day

Severity:

☐ 1. Mild – hallucinations are present but harmless and cause little distress for the patient.
☐ 2. Moderate – hallucinations are distressing and disruptive to the patient.
☐ 3. Marked – hallucinations are very disruptive and are a major source of behavioral disturbance. PRN medications may be required to control them.

Distress: How emotionally distressing do you find this behavior?

☐ 0. Not at all
☐ 1. Minimally
☐ 2. Mildly
☐ 3. Moderately
☐ 4. Severely
☐ 5. Very severely or extremely

NEUROPSYCHIATRIC INVENTORY (NPI)

Baseline and Visits 2 through 7

C. AGITATION/AGGRESSION (NA)

Does the patient have periods when he/she refuses cooperate or won't let people help him/her? Is he/she hard handle?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐ N/A

1.	Does the patient get upset with those trying to care for him/her or resist activities such as bathing or changing clothes?	☐ Yes	☐ No
2.	Is the patient stubborn, having to have things his/her way?	☐ Yes	☐ No
3.	Is the patient uncooperative, resistive to help from others?	☐ Yes	☐ No
4.	Does the patient have any other behaviors that make him/her hard to handle?	☐ Yes	☐ No
5.	Does the patient shout or curse angrily?	☐ Yes	☐ No
6.	Does the patient slam doors, kick furniture, throw things?	☐ Yes	☐ No
7.	Does the patient attempt to hurt or hit others?	☐ Yes	☐ No
8.	Does the patient have any other aggressive or agitated behaviors?	☐ Yes	☐ No

Comments: _____

_____

If the screening question is confirmed, determine the frequency and severity of the agitation/aggression (based on the most frequent symptom).

Frequency:

☐ 1. Occasionally – less than once per week
☐ 2. Often – about once per week
☐ 3. Frequently– several times per week but less than every day
☐ 4. Very frequently – once or more per day

Severity:

☐ 1. Mild – behavior is disruptive but can be managed with redirection or reassurance.
☐ 2. Moderate – behaviors are disruptive difficult to redirect or control.
☐ 3. Marked – agitation is very disruptive and a major source of difficulty; there may be a threat of personal harm. Medications are often required.

Distress: How emotionally distressing do you find this behavior?

☐ 0. Not at all
☐ 1. Minimally
☐ 2. Mildly
☐ 3. Moderately
☐ 4. Severely
☐ 5. Very severely or extremely

NEUROPSYCHIATRIC INVENTORY (NPI)

Baseline and Visits 2 through 7

D. DEPRESSION/DYSPHORIA (NA)

Does the patient seem sad or depressed? Does he/she say that he/she feels sad or depressed? Does the patient cry at times?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐ N/A

1.	Does the patient cry at times?	☐ Yes	☐ No
2.	Does the patient say, or act like he/she is depressed?	☐ Yes	☐ No
3.	Does the patient put him/herself down or say that he/she feels like a failure?	☐ Yes	☐ No
4.	Does the patient say that he/she is a bad person or deserves to be punished?	☐ Yes	☐ No
5.	Does the patient seem very discouraged or say that he/she has no future?	☐ Yes	☐ No
6.	Does the patient say he/she is a burden to the family or that the family would be better off without him/her?	☐ Yes	☐ No
7.	Does the patient express a wish for death or talk about killing him/herself?	☐ Yes	☐ No
8.	Does the patient show any other signs of depression or sadness?	☐ Yes	☐ No

Comments: _____

_____

If the screening question is confirmed, determine the frequency and severity of the depression (based on the most frequent symptom).

Frequency:

☐ 1. Occasionally – less than once per week
☐ 2. Often – about once per week
☐ 3. Frequently– several times per week but less than every day
☐ 4. Very frequently – essentially continuously present

Severity:

☐ 1. Mild – depression is distressing but usually responds to redirection or reassurance.
☐ 2. Moderate – depression is distressing, depressive symptoms are spontaneously voiced by the patient and difficult to alleviate.
☐ 3. Marked – depression is very distressing and a major source of suffering for the patient.

Distress: How emotionally distressing do you find this behavior?

☐ 0. Not at all
☐ 1. Minimally
☐ 2. Mildly
☐ 3. Moderately
☐ 4. Severely
☐ 5. Very severely or extremely

NEUROPSYCHIATRIC INVENTORY (NPI)

Baseline and Visits 2 through 7

E. ANXIETY (NA)

Is the patient very nervous, worried, or frightened for no reason? Does he/she seem very tense or fidgety? Is the patient afraid to be apart from you?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐ N/A

1.	Does the patient say that he/she is worried about planned events?	☐ Yes	☐ No
2.	Does the patient have periods of feeling shaky, unable to relax, or feeling excessively tense?	☐ Yes	☐ No
3.	Does the patient have periods of (or complain of) shortness of breath, gasping, or sighing for no apparent reason other than being nervousness?	☐ Yes	☐ No
4.	Does the patient complain of butterflies in his/her stomach, or of racing or pounding of the heart in association with nervousness? (Symptoms not explained by ill health)	☐ Yes	☐ No
5.	Does the patient avoid certain places or situations that make him/her more nervous such as riding in the car, meeting with friends, or being in crowds?	☐ Yes	☐ No
6.	Does the patient become nervous and upset when separated from your [or his/her caregiver]? (Does he/she cling to you to keep from being separated?)	☐ Yes	☐ No
7.	Does the patient show any other signs of anxiety?	☐ Yes	☐ No

Comments: _____

_____

If the screening question is confirmed, determine the frequency and severity of the anxiety (based on the most frequent symptom).

Frequency:

☐ 1. Occasionally – less than once per week
☐ 2. Often – about once per week
☐ 3. Frequently– several times per week but less than every day
☐ 4. Very frequently – once or more per day

Severity:

☐ 1. Mild – anxiety is distressing but usually responds to redirection or reassurance.
☐ 2. Moderate – anxiety is distressing, anxiety symptoms are spontaneously voiced by the patient and difficult to alleviate.
☐ 3. Marked – anxiety is very distressing and a major source of suffering for the patient.

Distress: How emotionally distressing do you find this behavior?

☐ 0. Not at all
☐ 1. Minimally
☐ 2. Mildly
☐ 3. Moderately
☐ 4. Severely
☐ 5. Very severely or extremely

NEUROPSYCHIATRIC INVENTORY (NPI)

Baseline and Visits 2 through 7

F. ELATION/EUPHORIA (NA)

Does the patient seem too cheerful or too happy for no reason? I don't mean normal happiness that comes from seeing friends, receiving presents, or spending time with family m embers. I am asking if the patient has a persistent and abnormally good mood or finds humor where others do not.

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐ N/A

1.	Does the patient appear to feel too good or to be too happy, different from his/her usual self?	☐ Yes	☐ No
2.	Does the patient find humor and laugh at things that others do not find funny?	☐ Yes	☐ No
3.	Does the patient seem to have a childish sense of humor with a tendency to giggle or laugh inappropriately (such as when something unfortunate happens to others)?	☐ Yes	☐ No
4.	Does the patient tell jokes or make remarks that have little humor for others but seem funny to him/her?	☐ Yes	☐ No
5.	Does he/she play childish pranks such as pinching or playing "keep away" for the fun of it?	☐ Yes	☐ No
6.	Does the patient "talk big" or claim to have abilities or wealth than is true?	☐ Yes	☐ No
7.	Does the patient show any other signs of feeling too good or being too happy?	☐ Yes	☐ No

Comments: _____

_____

If the screening question is confirmed, determine the frequency and severity of the elation/euphoria (based on the most frequent symptom).

Frequency:

☐ 1. Occasionally – less than once per week
☐ 2. Often – about once per week
☐ 3. Frequently– several times per week but less than every day
☐ 4. Very frequently – essentially continuously present

Severity:

☐ 1. Mild – elation is notable to friends and family but is not disruptive.
☐ 2. Moderate – elation is notably abnormal.
☐ 3. Marked – elation is very pronounced; patient is euphoric and finds nearly everything to be humorous.

Distress: How emotionally distressing do you find this behavior?

☐ 0. Not at all
☐ 1. Minimally
☐ 2. Mildly
☐ 3. Moderately
☐ 4. Severely
☐ 5. Very severely or extremely

NEUROPSYCHIATRIC INVENTORY (NPI)

Baseline and Visits 2 through 7

G. APATHY/INDIFFERENCE (NA)

Has the patient lost interest in the world around him/her? Has he/she lost interest in doing things or does he/she lack motivation for starting new activities? Is he/she more difficult to engage in conversation or in doing chores? Is this apathetic or indifferent?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐ N/A

1.	Does the patient seem less spontaneous and less active than usual?	☐ Yes	☐ No
2.	Is the patient less likely to initiate a conversation?	☐ Yes	☐ No
3.	Is the patient less affectionate or lacking in emotions when compared to his/her usual self?	☐ Yes	☐ No
4.	Does the patient contribute less to household chores?	☐ Yes	☐ No
5.	Does the patient seem less interested in the activities and plans of others?	☐ Yes	☐ No
6.	Has the patient lost interest in friends and family members?	☐ Yes	☐ No
7.	Is the patient less enthusiastic about his/her usual interests?	☐ Yes	☐ No
8.	Does the patient show any other signs that he/she doesn't care about doing new things?	☐ Yes	☐ No

Comments: _____

_____

If the screening question is confirmed, determine the frequency and severity of the apathy/indifference (based on the most frequent symptom).

Frequency:

☐ 1. Occasionally – less than once per week
☐ 2. Often – about once per week
☐ 3. Frequently– several times per week but less than every day
☐ 4. Very frequently – nearly always present

Severity:

☐ 1. Mild – apathy is notable but produces little interference with daily routines; only mildly different from patient's usual behavior; patient responds to suggestions to engage in activities.
☐ 2. Moderate – apathy is very evident; may be overcome by the caregiver with coaxing and encouragement; responds spontaneously only to powerful events such as visits from close relatives or family members.
☐ 3. Marked – apathy is very evident and usually fails to respond to any encouragement or external events.

Distress: How emotionally distressing do you find this behavior?

☐ 0. Not at all
☐ 1. Minimally
☐ 2. Mildly
☐ 3. Moderately
☐ 4. Severely
☐ 5. Very severely or extremely

NEUROPSYCHIATRIC INVENTORY (NPI)

Baseline and Visits 2 through 7

H. DISINHIBITION (NA)

Does the patient see to act impulsively without thinking? Does he/she do or say things that are not usually done or said in public? Does he/she do things that are embarrassing to you or others?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐ N/A

1.	Does the patient act impulsively without appearing to consider the consequences?	☐ Yes	☐ No
2.	Does the patient talk to total strangers as if he/she knew them?	☐ Yes	☐ No
3.	Does the patient say things to people that are insensitive or hurt their feelings?	☐ Yes	☐ No
4.	Does the patient say crude things or make sexual remarks that he/she would not usually have said?	☐ Yes	☐ No
5.	Does the patient talk openly about very personal or private matters not usually discussed in public?	☐ Yes	☐ No
6.	Does the patient take liberties or touch or hug others in way that is out of character for him/her?	☐ Yes	☐ No
7.	Does the patient show any other signs or loss of control of his/her impulses?	☐ Yes	☐ No

Comments: _____

_____

If the screening question is confirmed, determine the frequency and severity of the disinhibition (based on the most frequent symptom).

Frequency:

☐ 1. Occasionally – less than once per week
☐ 2. Often – about once per week
☐ 3. Frequently– several times per week but less than every day
☐ 4. Very frequently – essentially continuously present

Severity:

☐ 1. Mild – disinhibition is notable but usually responds to redirection or guidance.
☐ 2. Moderate – disinhibition is very evident and difficult to overcome by the caregiver.
☐ 3. Marked – disinhibition usually fails to respond to any intervention by the caregiver, and is a source of embarrassment or social distress.

Distress: How emotionally distressing do you find this behavior?

☐ 0. Not at all
☐ 1. Minimally
☐ 2. Mildly
☐ 3. Moderately
☐ 4. Severely
☐ 5. Very severely or extremely

NEUROPSYCHIATRIC INVENTORY (NPI)

Baseline and Visits 2 through 7

I. IRRITIABILITY/LABILITY (NA)

Does the patient get irritated and easily disturbed? Are his/her moods very changeable? Is he/she abnormally impatient? We do not mean frustration over memory loss or inability to perform usual tasks; we are interested to know if the patient has abnormal irritability, impatience, or rapid emotional changes different from his/her usual self.

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐ N/A

1.	Does the patient have a bad temper, flying "off the handle" easily over little things?	☐ Yes	☐ No
2.	Does the patient rapidly change moods from one to another, being fine one minute and angry the next?	☐ Yes	☐ No
3.	Does the patient have sudden flashes of anger?	☐ Yes	☐ No
4.	Is the patient impatient, having trouble coping with delays or waiting for planned activities or other things?	☐ Yes	☐ No
5.	Is the patient cranky and irritable?	☐ Yes	☐ No
6.	Is the patient argumentative and difficult to get along with?	☐ Yes	☐ No
7.	Does the patient show any other signs of irritability?	☐ Yes	☐ No

Comments: _____

_____

If the screening question is confirmed, determine the frequency and severity of the irritability/lability (based on the most frequent symptom).

Frequency:

☐ 1. Occasionally – less than once per week
☐ 2. Often – about once per week
☐ 3. Frequently– several times per week but less than every day
☐ 4. Very frequently – essentially continuously present

Severity:

☐ 1. Mild – irritability or lability is notable but usually responds to redirection and reassurance.
☐ 2. Moderate – irritability and lability are very evident and difficult to overcome by the caregiver.
☐ 3. Marked – irritability and lability are very evident, they usually fail to respond to any intervention by the caregiver, and they are a major source of distress.

Distress: How emotionally distressing do you find this behavior?

☐ 0. Not at all
☐ 1. Minimally
☐ 2. Mildly
☐ 3. Moderately
☐ 4. Severely
☐ 5. Very severely or extremely

NEUROPSYCHIATRIC INVENTORY (NPI)

Baseline and Visits 2 through 7

J. ABERRANT MOTOR BEHAVIOR (NA)

Does the patient pace, do things over and over such as opening closets or drawers, or repeatedly pick at things or wind string or threads?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐ N/A

1.	Does the patient pace around the house without apparent purpose?	☐ Yes	☐ No
2.	Does the patient rummage around opening and unpacking drawers or closets?	☐ Yes	☐ No
3.	Does the patient repeatedly put on and take off clothing?	☐ Yes	☐ No
4.	Does the patient have repetitive activities or "habits" that he/she performs over and over?	☐ Yes	☐ No
5.	Does the patient engage in repetitive activities such as handling buttons, picking, wrapping string, etc.?	☐ Yes	☐ No
6.	Does the patient fidget excessively, seem unable to sit still, or bounce his/her feet or tap his/her fingers a lot?	☐ Yes	☐ No
7.	Does the patient do any other activities over and over?	☐ Yes	☐ No

Comments: _____

_____

If the screening question is confirmed, determine the frequency and severity of the aberrant motor activity (based on the most frequent symptom).

Frequency:

☐ 1. Occasionally – less than once per week
☐ 2. Often – about once per week
☐ 3. Frequently– several times per week but less than every day
☐ 4. Very frequently – essentially continuously present

Severity:

☐ 1. Mild – abnormal motor activity is notable but produces little interference with daily routines.
☐ 2. Moderate – abnormal motor activity is very evident; can be overcome by the caregiver.
☐ 3. Marked – abnormal motor activity is very evident, usually fails to respond to any intervention by the caregiver, and is a major source of distress.

Distress: How emotionally distressing do you find this behavior?

☐ 0. Not at all
☐ 1. Minimally
☐ 2. Mildly
☐ 3. Moderately
☐ 4. Severely
☐ 5. Very severely or extremely

NEUROPSYCHIATRIC INVENTORY (NPI)

Baseline and Visits 2 through 7

K. SLEEP AND NIGHTTIME BEHAVIOR DISORDERS (NA)

Does the patient have difficulty sleeping (do not count as present if the patient simply gets up once or twice per night only to go to the bathroom and falls back asleep immediately)? Is he/she up at night? Does he/she wander at night, get dressed, or disturb your sleep?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐ N/A

1.	Does the patient have difficulty falling asleep?	☐ Yes	☐ No
2.	Does the patient get up during the night (do not count if the patient gets up once or twice per night only to go to the bathroom and falls back asleep immediately)?	☐ Yes	☐ No
3.	Does the patient wander, pace, or get involved in inappropriate activities at night?	☐ Yes	☐ No
4.	Does the patient awaken you during the night?	☐ Yes	☐ No
5.	Does the patient awaken at night, dress, and plan to go out, thinking that it is morning and time to start the day?	☐ Yes	☐ No
6.	Does the patient awaken too early in the morning (earlier than was his/her habit)?	☐ Yes	☐ No
7.	Does the patient sleep excessively during the day?	☐ Yes	☐ No
8.	Does the patient have any other nighttime behaviors that bother you that we haven't talked about?	☐ Yes	☐ No

Comments: _____

_____

If the screening question is confirmed, determine the frequency and severity of the nighttime behavior (based on the most frequent symptom).

Frequency:

☐ 1. Occasionally – less than once per week
☐ 2. Often – about once per week
☐ 3. Frequently– several times per week but less than every day
☐ 4. Very frequently – once or more per day (every night)

Severity:

☐ 1. Mild – nighttime behaviors occur but they are not particularly disruptive.
☐ 2. Moderate – nighttime behaviors occur and disturb the patient and the sleep of the caregiver; more than one type of nighttime behavior may be present.
☐ 3. Marked – nighttime behaviors occur; several types of nighttime behavior may be present; the patient is very distressed during the night and the caregiver's sleep is markedly disturbed.

Distress: How emotionally distressing do you find this behavior?

☐ 0. Not at all
☐ 1. Minimally
☐ 2. Mildly
☐ 3. Moderately
☐ 4. Severely
☐ 5. Very severely or extremely

NEUROPSYCHIATRIC INVENTORY (NPI)

Baseline and Visits 2 through 7

L. APPETITE AND EATING CHANGES (NA)

Has he/she had any change in appetite, weight, or eating habits (count as "N/A" if the patient is incapacitated and has to be fed)? Has there been any change in type of food he/she prefers?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐ N/A

1.	Does he/she have a loss of appetite?	☐ Yes	☐ No
2.	Has he/she had an increase in appetite?	☐ Yes	☐ No
3.	Has he/she had a loss of weight?	☐ Yes	☐ No
4.	Has he/she gained weight?	☐ Yes	☐ No
5.	Has he/she had a change in eating behavior such as putting too much food in his/her mouth at once?	☐ Yes	☐ No
6.	Has he/she had a change in the kind of food he/she likes such as eating too many sweets or other specific types of food?	☐ Yes	☐ No
7.	Has he/she developed eating behaviors such as eating exactly the same types of food each day or eating the food in exactly the same order?	☐ Yes	☐ No
8.	Have there been any other changes in appetite or eating that I haven't asked about?	☐ Yes	☐ No

Comments: _____

_____

If the screening question is confirmed, determine the frequency and severity of the changes in eating habits or appetite (based on the most frequent symptom).

Frequency:

☐ 1. Occasionally – less than once per week
☐ 2. Often – about once per week
☐ 3. Frequently– several times per week but less than every day
☐ 4. Very frequently – once or more per day or continuously

Severity:

☐ 1. Mild – changes in appetite or eating are present but have not led to changes in weight and are not disturbing.
☐ 2. Moderate – changes in appetite or eating are present and cause minor fluctuation in weight.
☐ 3. Marked – obvious changes in appetite or eating are present and cause fluctuations in weight, are embarrassing, or otherwise disturb the patient.

Distress: How emotionally distressing do you find this behavior?

☐ 0. Not at all
☐ 1. Minimally
☐ 2. Mildly
☐ 3. Moderately
☐ 4. Severely
☐ 5. Very severely or extremely

NEUROPSYCHIATRIC INVENTORY (NPI)

Baseline and Visits 2 through 7

SITE NUMBER	PATIENT NUMBER	PATIENT INITIALS	VISIT NUMBER	VISIT DATE	EXAMINER INITIALS

Please transcribe appropriate categories from the NPI-NH Worksheet into the boxes provided.

For each domain:

- If symptoms of a domain did not apply, check the "N/A" box.
- If symptoms of a domain were absent, check the "0" box.
- If symptoms of a domain were present, check one score each for Frequency and Severity (based on the most frequent symptom).
- Multiply Frequency score x Severity score and enter the product in the space provided.
- Total all Frequency x Severity scores and record the Total Score below.
- If symptoms of a domain were present, check one score for Occupational Disruptiveness; total all occupational disruptiveness scores for a summary score.

DOMAIN	N/A[1]	ABSENT	FREQUENCY	SEVERITY	FREQUENCY X SEVERITY	DISTRESS
		0	1 2 3 4	1 2 3		0 1 2 3 4 5
A. Delusions	☐	☐	☐	☐	☐☐	☐
B. Hallucinations	☐	☐	☐	☐	☐☐	☐
C. Agitation/Aggression	☐	☐	☐	☐	☐☐	☐
D. Depression/Dysphoria	☐	☐	☐	☐	☐☐	☐
E. Anxiety	☐	☐	☐	☐	☐☐	☐
F. Elation/Euphoria	☐	☐	☐	☐	☐☐	☐
G. Apathy/Indifference	☐	☐	☐	☐	☐☐	☐
H. Disinhibition	☐	☐	☐	☐	☐☐	☐
I. Irritability/Lability	☐	☐	☐	☐	☐☐	☐
J. Aberrant Motor Behavior	☐	☐	☐	☐	☐☐	☐
K. Sleep and Nighttime Behavior Disorders	☐	☐	☐	☐	☐☐	☐
L. Appetite/Eating Changes	☐	☐	☐	☐	☐☐	☐
TOTAL SCORE:					☐☐	☐

Appendix 4: Mini-Mental State Examination (MMSE) Sample

MMSE

Date of Examination ____/____/____ Examiner _____

Name _____ Age _____ Years of School Completed _____

Instructions: Words in boldface type should be read aloud clearly and slowly to the examinee. Item substitutions appear in parentheses. Administration should be conducted privately and in the examinee's primary language. Circle 0 if the response is incorrect, or 1 if the response is correct. Begin by asking the following two questions:

Do you have any trouble with your memory? **May I ask you some questions about your memory?**

ORIENTATION TO TIME		RESPONSE	SCORE (circle one)	
What is the...	**year?**		0	1
	season?		0	1
	month of the year?		0	1
	day of the week?		0	1
	date?		0	1

ORIENTATION TO PLACE*

Where are we now? What is the...

state (province)**?**		0	1
county (or city/town)**?**		0	1
city/town (or part of city/neighborhood)**?**		0	1
building (name or type)**?**		0	1
floor of the building (room number or address)**?**		0	1

*Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted.

REGISTRATION*

Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are... APPLE [*pause*], **PENNY** [*pause*], **TABLE** [*pause*]. **Now repeat those words back to me.**

[*Repeat up to 5 times, but score only the first trial.*]

APPLE		0	1
PENNY		0	1
TABLE		0	1

Now keep those words in mind. I am going to ask you to say them again in a few minutes.

*Alternative word sets (e.g., PONY, QUARTER, ORANGE) may be substituted and noted when retesting an examinee.

ATTENTION AND CALCULATION [*Serial 7s*]*

Now I'd like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop.

What is 100 take away 7?	[93]		0	1
If needed, say: **Keep going.**	[86]		0	1
If needed, say: **Keep going.**	[79]		0	1
If needed, say: **Keep going.**	[72]		0	1
If needed, say: **Keep going.**	[65]		0	1

*Alternative item (WORLD backward) should only be administered if the examinee refuses to perform the Serial 7s task. →

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Substitute and score this item only if the examinee refuses to perform the Serial 7s task.

Spell WORLD forward, then backward.
Correct forward spelling if misspelled,
but score only the backward spelling.

(D = 1)	(L = 1)	(R = 1)	(O = 1)	(W = 1)	(0 to 5)
____	____	____	____	____	____

RECALL

	RESPONSE	SCORE (circle one)
What were those three words I asked you to remember? [*Do not offer any hints.*]		
APPLE	_____	0 1
PENNY	_____	0 1
TABLE	_____	0 1

NAMING*

What is this? [*Point to a pencil or pen.*]	_____	0 1
What is this? [*Point to a watch.*]	_____	0 1

*Alternative common objects (e.g., eyeglasses, chair, keys) may be substituted and noted.

REPETITION

Now I am going to ask you to repeat what I say. Ready? "NO IFS, ANDS, OR BUTS." Now you say that.
[*Repeat up to 5 times, but score only the first trial.*]

NO IFS, ANDS, OR BUTS.	_____	0 1

Detach the next page along the lengthwise perforation, and then tear it in half along the horizontal perforation. Use the upper half of the page (blank) for the Comprehension, Writing, and Drawing items that follow. Use the lower half of the page as a stimulus form for the Reading ("CLOSE YOUR EYES") and Drawing (intersecting pentagons) items.

COMPREHENSION

Listen carefully because I am going to ask you to do something.
Take this paper in your right hand [*pause*], **fold it in half** [*pause*], **and put it on the floor (*or* table).**

TAKE IN RIGHT HAND	_____	0 1
FOLD IN HALF	_____	0 1
PUT ON FLOOR (*or* TABLE)	_____	0 1

READING

Please read this and do what it says. [*Show examinee the words on the stimulus form.*]

CLOSE YOUR EYES	_____	0 1

WRITING

Please write a sentence. [*If examinee does not respond, say:* **Write about the weather.**] 0 1

Place the blank piece of paper (unfolded) in front of the examinee and provide a pen or pencil. Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling.

DRAWING

Please copy this design. [*Display the intersecting pentagons on the stimulus form.*] 0 1

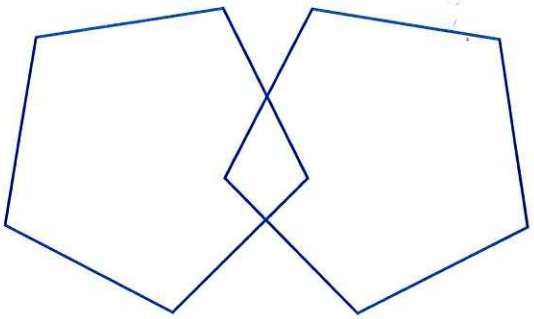
Score 1 point if the drawing consists of two 5-sided figures that intersect to form a 4-sided figure.

Total Score = _____
(*Sum all item scores.*) (30 points max.)

Assessment of level of consciousness.

Alert/ Responsive	Drowsy	Stuporous	Comatose/ Unresponsive

CLOSE YOUR EYES



Appendix 5: Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (ADCS-ADL) Sample

ALZHEIMER'S DISEASE COOPERATIVE STUDY – ACTIVITES OF DAILY LIVING SEVERE DEMENTIA VERSION (ADCS-ADL)

SITE NUMBER	PATIENT NUMBER	PATIENT INITIALS	VISIT NUMBER	VISIT DATE	EXAMINER INITIALS

INSTRUCTIONS: For each question, use the patient's name where {S} appears. Before beginning, read the questionnaire guidelines.

1. Regarding **eating**, which best describes {S} usual performance during the last 4 weeks?
   - ☐ 3 = ate without physical help, and used a knife
   - ☐ 2 = used a fork or spoon, but not a knife to eat
   - ☐ 1 = used fingers to eat
   - ☐ 0 = usually or always was fed by someone else
2. Regarding **walking** (or getting around in a wheelchair) in the past 4 weeks, which best describes {s} optimal performance?
   - ☐ 3 = mobile outside of home without physical help
   - ☐ 2 = mobile across a room without physical help
   - ☐ 1 = transferred from bed to chair without help
   - ☐ 0 = required physical help to walk and transfer
3. Regarding **bowel and bladder** function **at the toilet,** which best describes {S} usual performance during the past 4 weeks?
   - ☐ 3 = did everything necessary without supervision or help
   - ☐ 2 = needed supervision, but no physical help
   - ☐ 1 = needed physical help, and was usually continent
   - ☐ 0 = needed physical help, and was usually incontinent
4. Regarding **bathing**, in the past 4 weeks, which best describes {S} usual performance?
   - ☐ 3 = bathed without reminding or physical help
   - ☐ 2 = no physical help, but needed supervision/reminders to bathe completely
   - ☐ 1 = needed minor physical help (e.g., with washing hair) to bathe completely
   - ☐ 0 = needed to be bathed completely
5. Regarding **grooming**, in the past 4 weeks, which best describes {S} optimal performance?
   - ☐ 3 = cleaned and cut fingernails without physical help
   - ☐ 2 = brushed and combed hair without physical help
   - ☐ 1 = kept face and hands clean without physical help
   - ☐ 0 = needed help for grooming of hair, face, hands and fingernails

Used with permission from the NIA Alzheimer's Disease Cooperative Study (NIA Grant AG10483)

Reference: Galasko, D.; Bennett, D.; Sano, M.; Ernesto, C.; Thomas, R.; Grundman, M.; Ferris, S.; and the ADCS. "An Inventory to Assess Activities of Daily Living for Clinical Trials in Alzheimer's Disease." Alzheimer's Disease and Associated Disorders, 1997. Volume 11(2): S33-S39

ALZHEIMER'S DISEASE COOPERATIVE STUDY – ACTIVITES OF DAILY LIVING SEVERE DEMENTIA VERSION (ADCS-ADL)

6. Regarding **physically getting dressed**, which best describes {S} usual performance in the past 4 weeks?
   - □ 4 = dressed completely without supervision or physical help
   - □ 3 = dressed completely with supervision, but without help
   - □ 2 = needed physical help only for buttons, clasps, or shoelaces
   - □ 1 = dressed without help if clothes needed no fastening or buttoning
   - □ 0 = always needed help, regardless of clothing type

7. In the past 4 weeks, did {S} **use a telephone**?
   - □ 0 = No
   - □ 0 = Don't know
   - □ Yes; which best describes {S} **highest** level of performance:
     - □ 5 = made calls after looking up numbers in white or yellow pages, or by dialing directory assistance
     - □4 = made calls **only** to well-known numbers, **without** referring to a directory or list
     - □ 3 = made calls **only** to well-known numbers, **by using** a directory or list
     - □ 2 = answered the phone; did not make calls
     - □ 1 = did not answer the phone, but spoke when put on the line

8. In the past 4 weeks, did {S} watch television?
   - □ 0 = No
   - □ 0 = Don't know
   - □ Yes; **ask all questions**:
     Did {s}:
     a. usually select or ask for different programs or {S} favorite show?
        - □ 2 = Yes
        - □ 0 = No
     b. usually talk about the content of a program while watching it??
        - □ 1 = Yes
        - □ 0 = No
     c. talk about the content of a program within a day (24 hours) after watching it?
        - □ 1 = Yes
        - □ 0 = No

Used with permission from the NIA Alzheimer's Disease Cooperative Study (NIA Grant AG10483)

Reference: Galasko, D.; Bennett, D.; Sano, M.; Ernesto, C.; Thomas, R.; Grundman, M.; Ferris, S.; and the ADCS. "An Inventory to Assess Activities of Daily Living for Clinical Trials in Alzheimer's Disease." Alzheimer's Disease and Associated Disorders, 1997. Volume 11(2): S33-S39

ALZHEIMER'S DISEASE COOPERATIVE STUDY – ACTIVITES OF DAILY LIVING SEVERE DEMENTIA VERSION (ADCS-ADL)

9. In the past 4 weeks, did {S} ever appear to **pay attention to conversation or small talk** for at least 5 minutes?

   Note: *{S} did not need to initiate the conversation*

   □ 0 = No
   □ 0 = Don't know

   □ Yes; which best describes {S} usual degree of participation:
   - □ 3 = **usually** said things that were related to the topic
   - □ 2 = **usually** said things that were not related to the topic
   - □ 1 = rarely or never spoke

10. Did {S} clear the dishes from the table after a meal or snack?

    □ 0 = No
    □ 0 = Don't know

    □ Yes; which best describes {S} usually performed:
    - □ 3 = without supervision or help
    - □ 2 = with supervision
    - □ 1 = with physical help

11. In the past 4 weeks, did {S} usually manage to **find his/her personal belongings** at home?

    □ 0 = No
    □ 0 = Don't know

    □ Yes; which best describes {S} usually performed:
    - □ 3 = without supervision or help
    - □ 2 = with supervision
    - □ 1 = with physical help

12. In the past 4 weeks, did {S} **obtain a hot or cold beverage** for him/herself? *(A cold beverage includes a glass of water.)*

    □ 0 = No
    □ 0 = Don't know

    □ Yes; which best describes {S} highest level of performance:
    - □ 3 = made a hot beverage, usually without physical help
    - □ 2 = made a hot beverage, usually if someone else heated the water
    - □ 1 = obtained a cold beverage, usually without physical help

Reference: Galasko, D.; Bennett, D.; Sano, M.; Ernesto, C.; Thomas, R.; Grundman, M.; Ferris, S.; and the ADCS. "An Inventory to Assess Activities of Daily Living for Clinical Trials in Alzheimer's Disease." Alzheimer's Disease and Associated Disorders, 1997. Volume 11(2): S33-S39

13. In the past 4 weeks, did {S} **dispose of garbage or litter** in an appropriate place or container at home?
    - □ 0 = No
    - □ 0 = Don't know
    - □ Yes; which best describes {S} usually performed:
      - □ 3 = without supervision or help
      - □ 2 = with supervision
      - □ 1 = with physical help

14. In the past 4 weeks, did {S} **get around** (or travel) **outside of his/her home**?
    - □ 0 = No
    - □ 0 = Don't know
    - □ Yes; which best describes {S} optimal performance:
      - □ 4 = alone, went at least 1 mile away from home
      - □ 3 = alone, but remained within 1 mile of home
      - □ 2 = only when accompanied and supervised, regardless of the trip
      - □ 1 = only with physical help, regardless of the trip

15. In the past 4 weeks, was {S} ever **left on his/her own**?
    - □ 0 = No
    - □ 0 = Don't know
    - □ Yes; **ask all questions**:
      Was{S} left:
      a. away from home for 15 minutes or longer during the day?
         - □ 1 = Yes
         - □ 0 = No
      b. at home for an hour or longer during the day?
         - □ 1 = Yes
         - □ 0 = No
      c. at home for less than 1 hour during the day?
         - □ 1 = Yes
         - □ 0 = No

Reference: Galasko, D.; Bennett, D.; Sano, M.; Ernesto, C.; Thomas, R.; Grundman, M.; Ferris, S.; and the ADCS. "An Inventory to Assess Activities of Daily Living for Clinical Trials in Alzheimer's Disease." Alzheimer's Disease and Associated Disorders, 1997. Volume 11(2): S33-S39

16. In the past 4 weeks, did {S} usually run water from a faucet to wash {S} hands or face without help?
    - ☐ 1 = Yes
    - ☐ 0 = No
17. In the past 4 weeks, did {S} usually turn off the faucet after finishing running water without help?
    - ☐ 1 = Yes
    - ☐ 0 = No
18. In the past 4 weeks, did {S} usually turn on a light without help when entering a dark room or area?
    - ☐ 1 = Yes
    - ☐ 0 = No
19. In the past 4 weeks, did {S} usually turn off lights without help when leaving a room or going to sleep?
    - ☐ 1 = Yes
    - ☐ 0 = No

Used with permission from the NIA Alzheimer's Disease Cooperative Study (NIA Grant AG10483)

Reference: Galasko, D.; Bennett, D.; Sano, M.; Ernesto, C.; Thomas, R.; Grundman, M.; Ferris, S.; and the ADCS. "An Inventory to Assess Activities of Daily Living for Clinical Trials in Alzheimer's Disease." Alzheimer's Disease and Associated Disorders, 1997. Volume 11(2): S33-S39

Appendix 6: The Cornell Scale for Depression in Dementia (CSDD) Sample

CORNELL SCALE FOR DEPRESSION IN DEMENTIA (CSDD)

Screening, Visits 4 and 7

SITE NUMBER	PATIENT NUMBER	PATIENT INITIALS	VISIT NUMBER	VISIT DATE	EXAMINER INITIALS

Inpatient _____ *Nursing Home Resident* _____ *Outpatient* _____

Scoring System

a = unable to evaluate 0 = absent 1 = mild or intermittent 2 = severe

Ratings should be based on symptoms and signs occurring during the week prior to interview. No score should be given in symptoms resulting from physical disability or illness.

A. Mood-Related Signs					
1. Anxiety: anxious expression, ruminations, worrying	a	0	1	2
2. Sadness: sad expression, sad voice, tearfulness	a	0	1	2
3. Lack of reactivity to pleasant events	a	0	1	2
4. Irritability: easily annoyed, short-tempered	a	0	1	2
B. Behavioral Disturbance					
5. Agitation: restlessness, handwringing, hairpulling	a	0	1	2
6. Retardation: slow movement, slow speech, slow reactions	a	0	1	2
7. Multiple physical complaints (score 0 if GI symptoms only)	a	0	1	2
8. Loss of interest: less involved in usual activities (score only if change occurred acutely, i.e. in less than 1 month)	a	0	1	2
C. Physical Signs					
9. Appetite loss: eating less than usual	a	0	1	2
10. Weight loss (score 2 if greater than 5 lb. in 1 month)	a	0	1	2
11. Lack of energy: fatigues easily, unable to sustain activities (score only if change occurred acutely, i.e., in less than 1 month)	a	0	1	2
D. Cyclic Functions					
12. Diurnal variation of mood: symptoms worse in the morning	a	0	1	2
13. Difficulty falling asleep: later than usual for this individual	a	0	1	2
14. Multiple awakenings during sleep	a	0	1	2
15. Early morning awakening: earlier than usual for this individual	a	0	1	2
E. Ideational Disturbance					
16. Suicide: feels life is not worth living, has suicidal wishes, or makes suicide attempt	a	0	1	2
17. Poor self esteem: self-blame, self-depreciation, feelings of failure	a	0	1	2
18. Pessimism: anticipation of the worst	a	0	1	2
19. Mood congruent delusions: delusions of poverty, illness, or loss	a	0	1	2

Reference: Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. Cornell Scale for Depression in Dementia. Biological Psychiatry. 1988;23(3):271-84.

Appendix 7: Caregiver Strain Index (CSI) Sample

CAREGIVER STRAIN INDEX (CSI)

Baseline and Visits 2 through 7

SITE NUMBER	PATIENT NUMBER	PATIENT INITIALS	VISIT NUMBER	VISIT DATE	EXAMINER INITIALS

The Caregiver Strain Index: I am going to read a list of things that other people have found to be difficult. Would you tell me if any of these apply to you? (Give examples)

	Yes = 1	No = 0
Sleep is disturbed (e.g., because _____ is in and out of bed or wanders around at night)		
It is inconvenient (e.g., because helping takes so much time or it's a long drive over to help)		
It is a physical strain (e.g. because of lifting in and out of a chair; effort or concentration is required)		
It is confining (e.g., helping restricts free time or cannot go visiting)		
There have been family adjustments (e.g., because helping has disrupted routine; there has been no privacy)		
There have been changes in personal plans (e.g., had to turn down a job; could not go on vacation)		
There have been other demands on my time (e.g., from other family members)		
There have been emotional adjustments (e.g., because of severe arguments)		
Some behavior is upsetting (e.g., because of incontinence; _____ has trouble remembering things; or _____ accuses people of taking things)		
It is upsetting to find _____ has changed so much from his/her former self (e.g., he/she is a different person than he/she used to be)		
There have been work adjustments (e.g., because of having to take time off)		
It is a financial strain		
Feeling completely overwhelmed (e.g., because of worry about _____; concerns about how you will manage)		

TOTAL SCORE: Count yes responses. Any positive answer may indicate a need for intervention in that area. A score of 7 or higher indicates a high level of stress.

Reference: Robinson, B. (1983). Validation of a Caregiver Strain Index. Journal of Gerontology. 38:344-348.

Appendix 8: Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-cog) Sample

ALZHEIMER'S DISEASE ASSESSMENT SCALE – COGNITIVE BEHAVIOR (ADAS-COG)

Baseline

SITE NUMBER	PATIENT NUMBER	PATIENT INITIALS	VISIT NUMBER	VISIT DATE	EXAMINER INITIALS

1. **WORD RECALL TASK:** Indicate the total number of words ***not recalled*** during each trial.

Trial 1	Trial 2	Trial 3

2. **Commands:** Check each command performed ***correctly*** or check "NONE".

- ☐ None
- ☐ Make a fist.
- ☐ Point to the ceiling, then to the floor.
- ☐ Put the pencil on top of the card, then put it back.
- ☐ Put the watch on the other side of the pencil and turn over the card.
- ☐ Tap each shoulder twice, with two fingers, keeping your eyes shut.

SCORING:
0 = all commands correct
1 = 1 command incorrect
2 = 2 commands incorrect
3 = 3 commands incorrect
4 = 4 commands incorrect
5 = all commands incorrect

Score = _____

3. **Constructional Praxis:** Check each figure drawn ***correctly.***

- ☐ None: attempted but drew no forms correctly
- ☐ Patient drew no forms; scribbled wrote words
- ☐ Circle
- ☐ Two overlapping rectangles
- ☐ Rhombus
- ☐ Cube

SCORING:
0 = all 4 drawings correct
1 = 1 form drawn incorrectly
2 = 2 forms drawn incorrectly
3 = 3 forms drawn incorrectly
4 = 4 forms drawn incorrectly (but one or more side/section of at least one shape drawn)
5 = No figures drawn, no recognizable attempt at drawing any side/section of any figure

Score = _____

4. **NAMING OBJECTS AND FINGERS:** Check each object/finger named ***correctly*** or check "NONE".

☐ None

☐ Flower	☐ Rattle	☐ Wallet
☐ Bed	☐ Mask	☐ Harmonica
☐ Whistle	☐ Scissors	☐ Stethoscope
☐ Pencil	☐ Comb	☐ Tongs
☐ Thumb	☐ Index	☐ Ring
☐ Pinky	☐ Middle	

SCORING:
0 = 0-2 items (objects and fingers) named incorrectly
1 = 3-5 items (objects and fingers) named incorrectly
2 = 6-8 items (objects and fingers) named incorrectly
3 = 9-11 items (objects and fingers) named incorrectly
4 = 12-14 items (objects and fingers) named incorrectly
5 = 15-17 items (objects and fingers) named incorrectly

Score = _____

ALZHEIMER'S DISEASE ASSESSMENT SCALE – COGNITIVE BEHAVIOR (ADAS-COG)

Baseline

5. **IDEATIONAL PRAXIS:** Check each step completed ***correctly*** or check "None". ☐ None ☐ Fold a letter ☐ Put letter in envelope ☐ Seal envelope ☐ Address envelope ☐ Indicate where the stamp goes	**SCORING:** 0 = all components performed correctly 1 = failure to perform 1 component 2 = failure to perform 2 components 3 = failure to perform 3 components 4 = failure to perform 4 components 5 = failure to perform 5 components **Score = _____**
6. **ORIENTATION:** Check each item answered ***correctly*** or check "None". ☐ None ☐ Full name ☐ Day ☐ Month ☐ Season ☐ Date ☐ Place ☐ Year ☐ Time of day	**SCORING:** One point is given for each incorrect response (maximum = 8). **Score = _____**
7. **WORD RECOGNITION:** Indicate the total number of ***incorrect*** responses (Max 24) **# Incorrect Words**	**SCORING:** There are 24 opportunities for error in the one trial of recognition, including the 12 learning (target) words and 12 distractor words. While all incorrect responses should be noted on the form by the rater (there are 0-24 errors possible in the trial), the maximum error score is 12. If the subject makes 13-24 errors, the score for the trial remains at 12. **Score = _____**
8. REMBERING TEST INSTRUCTIONS: Check level of impairment. ☐ **None** ☐ **Very Mild:** forgets once. ☐ **Mild:** must be reminded 2 times ☐ **Moderate:** must be reminded 3-4 times ☐ **Moderately Severe:** must be reminded 5-6 times ☐ **Severe:** must be reminded 7 or more times	**SCORING:** Based on the number of instruction repetitions only after the first two words. No other tasks or aspects of the ADAS-cog are considered when scoring this item. 0 = None 1 = very mild 2 = mild 3 = moderate 4 = moderately severe 5 = severe **Score = _____**
9. **COMPREHENSION OF SPOKEN LANGUAGE:** Check level of impairment. ☐ **None**: patient understands. ☐ **Very Mild:** one instance of misunderstanding . ☐ **Mild:** 3-5 instances of misunderstanding. ☐ **Moderate:** requires several repetitions and rephrasing. ☐ **Moderately Severe:** patient only occasionally responds correctly; i.e. yes-no questions ☐ **Severe:** patient rarely responds to questions appropriately; not due to poverty of speech	**SCORING:** 0 = None 1 = very mild 2 = mild 3 = moderate 4 = moderately severe 5 = severe **Score = _____**

Based on The Administration and Scoring Manual for the Alzheimer's Disease Assessment Scale, Revised 3/20/12

ALZHEIMER'S DISEASE ASSESSMENT SCALE – COGNITIVE BEHAVIOR (ADAS-COG)

Baseline

10. **WORD FINDING DIFFICULTY:** Check one response. ☐ **None** ☐ **Very Mild:** 1 or 2 instances, not clinically significant. ☐ **Mild:** noticeable circumlocution or synonym substitution. ☐ **Moderate:** loss of words without compensation on occasion. ☐ **Moderately Severe:** frequent loss of words without compensation. ☐ **Severe:** nearly total loss of content words; speech sounds empty; 1– to 2-word utterances.	**SCORING:** 0 = None 1 = very mild 2 = mild 3 = moderate 4 = moderately severe 5 = severe **Score = _____**
11. **SPOKEN LANGUAGE ABILITY:** Check level of impairment ☐ **None**: patient speaks clearly and/or is understandable. ☐ **Very Mild:** one instance of lack of understandability. ☐ **Mild:** patient has difficulty less than 25% of the time. ☐ **Moderate:** subject has difficulty 25-50% of the time ☐ **Moderately Severe:** subject has difficulty more than 50% of the time. ☐ **Severe:** one or two word utterances; fluent, but empty speech; mute	**SCORING:** This item is a global rating of the quality of speech, i.e., lack of clarity, difficulty in making oneself understood. 0 = None 1 = very mild 2 = mild 3 = moderate 4 = moderately severe 5 = severe **Score = _____**

ALZHEIMER'S DISEASE ASSESSMENT SCALE – COGNITIVE BEHAVIOR (ADAS-COG)

Baseline Word Recall

Present Word Recall List for Baseline

Check EACH word correctly recalled

Trial 1	
Butter	
Arm	
Shore	
Letter	
Queen	
Cabin	
Pole	
Ticket	
Grass	
Engine	

TOTAL CORRECT	
# Incorrect (10-# Correct)	

Trial 2	
Pole	
Letter	
Butter	
Queen	
Arm	
Shore	
Grass	
Cabin	
Ticket	
Engine	

TOTAL CORRECT	
# Incorrect (10-# Correct)	

Trial 3	
Shore	
Letter	
Arm	
Cabin	
Pole	
Ticket	
Engine	
Grass	
Butter	
Queen	

TOTAL CORRECT	
# Incorrect (10-# Correct)	

Based on The Administration and Scoring Manual for the Alzheimer's Disease Assessment Scale, Revised 3/20/12

ALZHEIMER'S DISEASE ASSESSMENT SCALE – COGNITIVE BEHAVIOR (ADAS-COG)

Baseline Word Recognition

Present Word Recognition for Baseline

Place a check in the appropriate column (Yes or No) for subject's response for each word. Subject should respond "yes" to original words which are bolded. INCORRECT responses would be marked in the shaded boxes.

	Yes	No	Reminder Given
Nurse			
Magazine			
Wizard			
Van			
Leopard			
Sale			
Sea			
Train			
Coin			
Ship			
Institution			
Map			
Axe			
Board			
Carrot			
Milk			
Volume			
Forest			
Anchor			
Gem			
Cat			
Fund			
Edge			
Cake			

	Number of Shaded Boxes Checked from Both Columns
TOTAL # Incorrect	

TOTAL Reminders Given	

Based on The Administration and Scoring Manual for the Alzheimer's Disease Assessment Scale, Revised 3/20/12

Appendix 9: Patient Global Impression of Change (PGI-C) Sample

PATIENT GLOBAL IMPRESSION OF CHANGE (RATED BY THE CAREGIVER) (PGI-C)

Visits 4 and 7

SITE NUMBER	PATIENT NUMBER	PATIENT INITIALS	VISIT NUMBER	VISIT DATE	EXAMINER INITIALS

Caregiver to check the one number that best describes the patient's agitation, whether or not in the judgment of the caregiver, the change is due entirely to drug treatment.

Compared to his/her condition at admission to the study, how much has he/she changed?

☐ 1 = Very much improved

☐ 2 = Much improved

☐ 3 = Minimally improved

☐ 4 = No change

☐ 5 = Minimally worse

☐ 6 = Much worse

☐ 7 = Very much worse

Appendix 10: Clinical Global Impression of Change (CGIC) Sample

MODIFIED ALZHEIMER'S DISEASE COOPERATIVE STUDY CLINICAL GLOBAL IMPRESSION OF CHANGE RATING (ADCS-CGIC)

Visit 4

SITE NUMBER	PATIENT NUMBER	PATIENT INITIALS	VISIT NUMBER	VISIT DATE	EXAMINER INITIALS

Clinical Impression of Change from Baseline – Status of Patient's Agitation Syndrome

- ☐ Marked Improvement
- ☐ Moderate Improvement
- ☐ Minimal Improvement
- ☐ No Change
- ☐ Minimal Worsening
- ☐ Moderate Worsening
- ☐ Marked Worsening

Clinical Impression of Change from Baseline – Patient's Overall Clinical Status

- ☐ Marked Improvement
- ☐ Moderate Improvement
- ☐ Minimal Improvement
- ☐ No Change
- ☐ Minimal Worsening
- ☐ Moderate Worsening
- ☐ Marked Worsening

Reference: Schneider, L.; Olin, J.; Doody, R.; Clark, C.; Morris, J.; Reisberg, B.; Schmitt, F.; Grundman, M.; Thomas, R.; Ferris, S.; and the ADCS. "Validity and Reliability of the Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change." *Alzheimer's Disease and Associated Disorders*, 1997. Vol 11(2): S22-S32.

MODIFIED ALZHEIMER'S DISEASE COOPERATIVE STUDY CLINICAL GLOBAL IMPRESSION OF CHANGE RATING (ADCS-CGIC)

Visit 7

Clinical Impression of Change from Baseline

Status of Patient's Agitation Syndrome	**Patient's Overall Clinical Status**
☐ Marked Improvement	☐ Marked Improvement
☐ Moderate Improvement	☐ Moderate Improvement
☐ Minimal Improvement	☐ Minimal Improvement
☐ No Change	☐ No Change
☐ Minimal Worsening	☐ Minimal Worsening
☐ Moderate Worsening	☐ Moderate Worsening
☐ Marked Worsening	☐ Marked Worsening

Clinical Impression of Change from Visit 4 Assessment

Status of Patient's Agitation Syndrome	**Patient's Overall Clinical Status**
☐ Marked Improvement	☐ Marked Improvement
☐ Moderate Improvement	☐ Moderate Improvement
☐ Minimal Improvement	☐ Minimal Improvement
☐ No Change	☐ No Change
☐ Minimal Worsening	☐ Minimal Worsening
☐ Moderate Worsening	☐ Moderate Worsening
☐ Marked Worsening	☐ Marked Worsening

Reference: Schneider, L.; Olin, J.; Doody, R.; Clark, C.; Morris, J.; Reisberg, B.; Schmitt, F.; Grundman, M.; Thomas, R.; Ferris, S.; and the ADCS. "Validity and Reliability of the Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change." *Alzheimer's Disease and Associated Disorders*, 1997. Vol 11(2): S22-S32.

Appendix 11: Quality of Life - Alzheimer's disease Measure (QoL-AD) Sample

QUALITY OF LIFE - AD
(QoL - AD)

Interview Version for the Person with Dementia

Baseline, Visits 4 and 7

SITE NUMBER	PATIENT NUMBER	PATIENT INITIALS	VISIT NUMBER	VISIT DATE	EXAMINER INITIALS

Interviewer administer according to standard instructions. Circle responses.				
1. Physical health	Poor	Fair	Good	Excellent
2. Energy	Poor	Fair	Good	Excellent
3. Mood	Poor	Fair	Good	Excellent
4. Living situation	Poor	Fair	Good	Excellent
5. Memory	Poor	Fair	Good	Excellent
6. Family	Poor	Fair	Good	Excellent
7. Marriage	Poor	Fair	Good	Excellent
8. Friends	Poor	Fair	Good	Excellent
9. Self as a whole	Poor	Fair	Good	Excellent
10. Ability to do chores around the house	Poor	Fair	Good	Excellent
11. Ability to do things for fun	Poor	Fair	Good	Excellent
12. Money	Poor	Fair	Good	Excellent
13. Life as a whole	Poor	Fair	Good	Excellent

Comments: _____

_____

_____

QUALITY OF LIFE - AD
(QoL - AD)

Questionnaire Version for the Family Member or Caregiver

Baseline, Visits 4 and 7

SITE NUMBER	PATIENT NUMBER	PATIENT INITIALS	VISIT NUMBER	VISIT DATE	EXAMINER INITIALS

The following questions are about your relative's quality of life.
When you think about your relative's life, there are different aspects, some of which are listed below. Please think about each item, and rate your relative's current quality of life in each area using one of four words: **poor, fair, good, or excellent**. Please rate these items based on your relative's life **at the present time** (e.g. within the past few weeks). If you have questions about any item, please ask the person who gave you this form for assistance.
Circle your responses.

1. Physical health	Poor	Fair	Good	Excellent
2. Energy	Poor	Fair	Good	Excellent
3. Mood	Poor	Fair	Good	Excellent
4. Living situation	Poor	Fair	Good	Excellent
5. Memory	Poor	Fair	Good	Excellent
6. Family	Poor	Fair	Good	Excellent
7. Marriage	Poor	Fair	Good	Excellent
8. Friends	Poor	Fair	Good	Excellent
9. Self as a whole	Poor	Fair	Good	Excellent
10. Ability to do chores around the house	Poor	Fair	Good	Excellent
11. Ability to do things for fun	Poor	Fair	Good	Excellent
12. Money	Poor	Fair	Good	Excellent
13. Life as a whole	Poor	Fair	Good	Excellent

Comments: _____

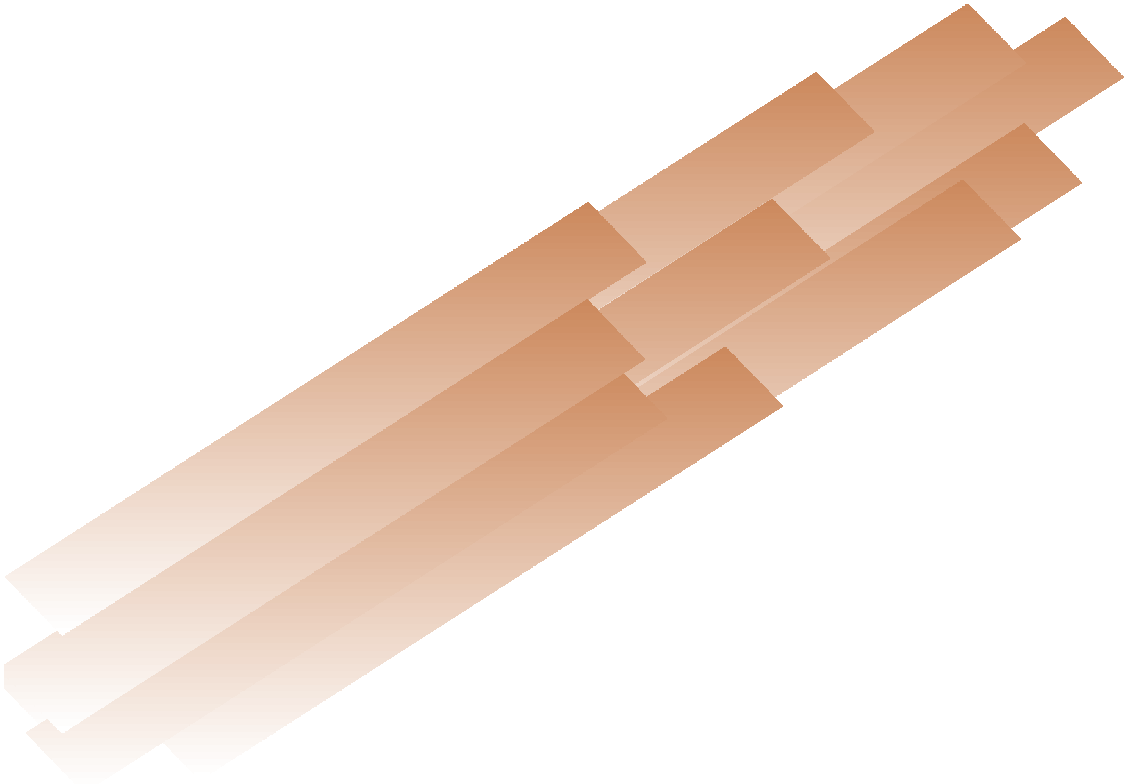
_____

_____

Appendix 12: Investigator Responsibilities

Guidance for Industry

E6 Good Clinical Practice: Consolidated Guidance



ICH
April 1996

Guidance for Industry

E6 Good Clinical Practice: Consolidated Guidance

Additional copies are available from:
the Drug Information Branch (HFD-210),
Center for Drug Evaluation and Research (CDER),
5600 Fishers Lane, Rockville, MD 20857 (Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm
or
Office of Communication,
Training, and Manufacturers Assistance (HFM-40)
Center for Biologics Evaluation and Research (CBER)
1401 Rockville Pike, Rockville, MD 20852-1448,
http://www.fda.gov/cber/guidelines.htm
(Fax) 888-CBERFAX or 301-827-3844
(Voice Information) 800-835-4709 or 301-827-1800

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
April 1996
ICH

(b) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial (see section 4.10.2).

(c) All adverse drug reactions (ADRs) that are both serious and unexpected.

(d) New information that may affect adversely the safety of the subjects or the conduct of the trial.

3.3.9 Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning:

(a) Its trial-related decisions/opinions.
(b) The reasons for its decisions/opinions.
(c) Procedures for appeal of its decisions/opinions.

3.4 Records

The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies).

The IRB/IEC may be asked by investigators, sponsors, or regulatory authorities to provide copies of its written procedures and membership lists.

4. INVESTIGATOR

4.1 Investigator's Qualifications and Agreements

4.1.1 The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).

4.1.2 The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information, and in other information sources provided by the sponsor.

4.1.3 The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

4.1.4 The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

4.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

4.2 Adequate Resources

4.2.1 The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

4.2.2 The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.2.3 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4.2.4 The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

4.3 Medical Care of Trial Subjects

4.3.1 A qualified physician (or dentist, when appropriate), who is an investigator or a subinvestigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

4.3.2 During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

4.3.3 It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

4.3.4 Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

4.4 Communication with IRB/IEC

4.4.1 Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

4.4.2 As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.

4.4.3 During the trial the investigator/institution should provide to the IRB/IEC all documents subject to its review.

4.5 Compliance with Protocol

4.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm their agreement.

4.5.2 The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s)).

4.5.3 The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

4.5.4 The investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented

deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) To the IRB/IEC for review and approval/favorable opinion;
(b) To the sponsor for agreement and, if required;
(c) To the regulatory authority(ies).

4.6 Investigational Product(s)

4.6.1 Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

4.6.2 Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

4.6.3 The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

4.6.4 The investigational product(s) should be stored as specified by the sponsor (see sections 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

4.6.5 The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

4.6.6 The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

4.7 Randomization Procedures and Unblinding

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded,

the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

4.8 Informed Consent of Trial Subjects

4.8.1 In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other written information to be provided to subjects.

4.8.2 The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favorable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

4.8.3 Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

4.8.4 None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

4.8.5 The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information given approval/favorable opinion by the IRB/IEC.

4.8.6 The language used in the oral and written information about the trial, including the written informed consent form, should be as nontechnical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

4.8.7 Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

4.8.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

4.8.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial, and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

(a) That the trial involves research.

(b) The purpose of the trial.

(c) The trial treatment(s) and the probability for random assignment to each treatment.

(d) The trial procedures to be followed, including all invasive procedures.

(e) The subject's responsibilities.

(f) Those aspects of the trial that are experimental.

(g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

(h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

(i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

(j) The compensation and/or treatment available to the subject in the event of trial-related injury.

(k) The anticipated prorated payment, if any, to the subject for participating in the trial.

(l) The anticipated expenses, if any, to the subject for participating in the trial.

(m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

(n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

(o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject’s identity will remain confidential.

(p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.

(q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.

(r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.

(s) The expected duration of the subject's participation in the trial.

(t) The approximate number of subjects involved in the trial.

4.8.11 Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

4.8.12 When a clinical trial (therapeutic or nontherapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should assent, sign and personally date the written informed consent.

4.8.13 Except as described in 4.8.14, a nontherapeutic trial (i.e., a trial in which there is no anticipated direct clinical benefit to the subject) should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

4.8.14 Nontherapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

(a) The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally.

(b) The foreseeable risks to the subjects are low.

(c) The negative impact on the subject's well-being is minimized and low.

(d) The trial is not prohibited by law.

(e) The approval/favorable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/favorable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

4.8.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrollment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favorable opinion by the IRB/IEC, to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see section 4.8.10) should be requested.

4.9 Records and Reports

4.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

4.9.2 Data reported on the CRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

4.9.3 Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes or corrections (see section 5.18.4(n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

4.9.4 The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see section 8.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

4.9.5 Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see section 5.5.12).

4.9.6 The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

4.9.7 Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

4.10 Progress Reports

4.10.1 Where required by the applicable regulatory requirements, the investigator should submit written summaries of the trial's status to the institution. The investigator/institution should submit written summaries of the status of the trial to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

4.10.2 The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see section 3.3.8), and, where required by the applicable regulatory requirements, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

4.11 Safety Reporting

4.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

4.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

4.11.3 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

4.12 Premature Termination or Suspension of a Trial

If the trial is terminated prematurely or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

4.12.1 If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.2 If the sponsor terminates or suspends a trial (see section 5.21), the investigator should promptly inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.3 If the IRB/IEC terminates or suspends its approval/favorable opinion of a trial (see sections 3.1.2 and 3.3.9), the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

4.13 Final Report(s) by Investigator/Institution

Upon completion of the trial, the investigator should, where required by the applicable regulatory requirements, inform the institution, and the investigator/institution should provide the sponsor with all required reports, the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any report(s) they require of the investigator/institution.

Appendix 13: World Medical Association Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy

volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

21Aug2014

Statistical Analysis Plan

Protocol 12-AVR-131

Version 1.1 (supercedes Version 1.0 dated 07Aug2014)

SIGNATURE PAGE

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1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AD	Alzheimer's Disease
ADAS-cog	Alzheimer's Disease Assessment Scale – cognitive subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory
ADCS-CGIC	Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change
ALT/SGPT	Alanine aminotransferase/serum glutamic-pyruvic transaminase
ANCOVA	Analysis of covariance
AR1	Auto-regressive (1)
ALT(SGPT)	Alanine aminotransferase (serum glutamic-pyruvate transaminase)
AST(SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
AUC0-12	Area under the curve 0-12 hours
BP	Blood Pressure
CGIS	Clinical Global Impression of Severity of Illness
CiTAD	Citalopram for agitation in Alzheimer's Disease
CMAI	Cohen Mansfield Agitation Inventory
CS	Compound symmetry
CSDD	Cornell Scale for Depression in Dementia
CSI	Caregiver Strain Index
Cmax	Maximum concentration
DBP	Diastolic Blood Pressure
DM	Dextromethorphan
DX	Dextromethorpan
ECG	Electrocardiogram
GGT	Gamma-glutamyltransferase
ITT	Intent-to-treat
LOCF	Last observation carried forward
MITT	Modified intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
Msec	Millisecond
MMSE	Min-Mental State Examination
NBRS-A	Neurobehavioral Rating Scale-agitation subscale
NPI	Neuropsychiatric Inventory
OLS	Ordinary Least Squares
PCS	Potentially clinically significant
PGI-C	Patient Global Impression of Change
PK	Pharmacokinetics
PR	The P-R interval from an ECG tracing
PT	Preferred Term
Q	Quinidine
QoL-AD	Quality of Life – Alzheimer's Disease Measure

Abbreviation	Definition
QRS	Q-R-S complex from an ECG tracing
QT	QT interval from an ECG tracing
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett's formula
QTcF	QT interval corrected for heart rate using the Fridericia's formula
RR	RR interval from an ECG tracing
SAF	Safety population
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SI units	International System of Units
SOC	System organ class
SPCD	Sequential Parallel Comparison Design
TEAE	Treatment-emergent Adverse Event

2.0 INTRODUCTION

2.1 Purpose of Statistical Analysis Plan

The purpose of this statistical analysis plan is to describe in detail the procedures and statistical methods required for completing the statistical analysis for Study 12-AVR-131 (Protocol Amendment 3, Version 4.0, dated 28 January 2014).

2.2 Study Objectives

2.2.1 Primary Objectives

The primary objective of the study is to evaluate the efficacy of AVP-923 compared to Placebo, for the treatment of symptoms of agitation in patients with Alzheimer's disease (AD). AVP-923 is a combination of dextromethorphan (DM) and quinidine (Q).

2.2.2 Secondary Objectives

The secondary objectives of the study are to evaluate the safety, tolerability, and pharmacokinetics (PK) of AVP-923 (AVP-923-20 and AVP-923-30) in patients with AD.

2.3 Summary of Study Design

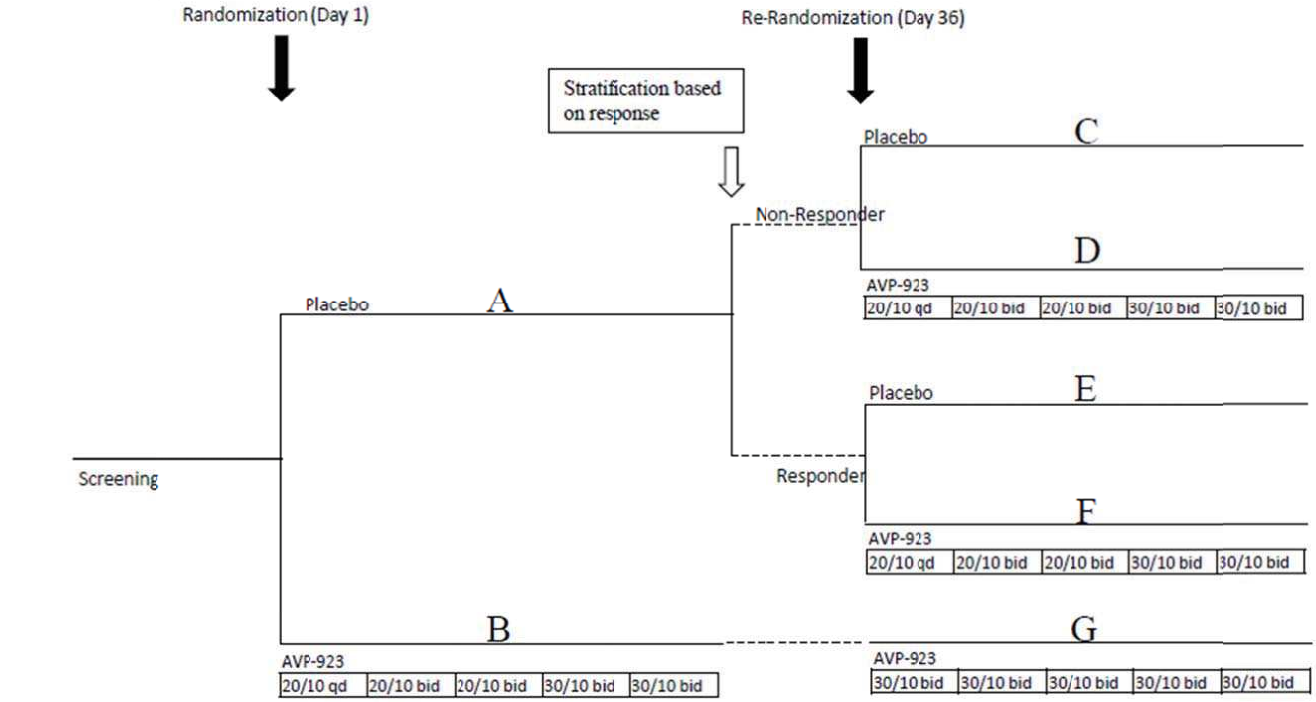
This is a multicenter, randomized, double-dummy, double-blind, placebo-controlled, 2-stage, sequential parallel study using the Sequential Parallel Comparison Design (SPCD)[1]. The study consists of 2 consecutive double-blind treatment stages (Stage 1 and Stage 2). Each stage is of 5-week duration. (See Figure 1 Study Schematic)

Up to approximately 200 patients will be enrolled at approximately 30 to 40 centers in the US.

Eligible patients will be randomly assigned at the Baseline visit to receive AVP-923 or matching Placebo. Study medication will be administered orally twice-daily from Day 1 through Day 70.

Screening procedures must occur within 4 weeks prior to randomization. Following screening procedures for assessment of inclusion and exclusion criteria, eligible patients will be randomized into Stage 1 of the study.

Figure 1: Study Schematic



Period	Screening		Stage 1				
Visit			B	V2		V3	
Day	-28	-7 -1	1 7	8 14	15 21	22 28	29 35
Week	Week-4	Week-1	Week 1	Week 2	Week 3	Week 4	Week 5

Stage 2				
V4	V5		V6	V7
36* 42	43 49	50 56	57 63	64 70
Week 6	Week 7	Week 8	Week 9	Week 10

*Day 36 (V4) assessments are part of Stage 1 and also serve as baseline assessments for Stage 2

Stage 1

Eligible patients will be randomized into Stage 1 of the study in a 3:4 (active:placebo) ratio to receive either AVP-923 capsules or matching Placebo capsules administered orally for 5 consecutive weeks. All patients receiving AVP-923 will start at AVP-923-20 (20 mg of DM and 10 mg of Q) once a day and be escalated up to AVP-923-30 (30 mg of DM and 10 mg of Q) twice a day (BID). For the initial 7 days of the study, randomized patients will receive AVP-923-20 in the morning and Placebo in the evening, or Placebo twice-a-day (Stage 1, Days 1-7). Starting on Day 8, patients will receive AVP-923-20 BID or Placebo BID for 2 consecutive weeks (Stage 1, Days 8-21), taking one capsule in the morning and one capsule in the evening, approximately 12 hours apart. On Day 22 of the study, the dose of study medication will be escalated in a double-blind manner. Patients receiving AVP-923-20 BID will increase to AVP-923-30 BID, and patients receiving Placebo BID will continue receiving Placebo for the remaining 2 weeks (Stage 1, Days 22-35) of the study. All study medication including AVP-923-20 capsules, AVP-923-30 capsules, and Placebo capsules are of identical appearance in order to maintain the integrity of the blind.

Stage 2

Patients who have completed Stage 1 are eligible to participate in the 5-week Stage 2 of the study. Study medication will be administered orally twice daily throughout Stage 2. Patients will be assigned to a double-blind treatment for additional 5 weeks as follows:

- Patients who received AVP-923 in Stage 1 (Days 1-35), will receive AVP-923-30 BID for the entire 5-week duration of Stage 2 (Days 36-70).

- Patients who received Placebo in Stage 1 will be stratified into two sub-groups ("responders" and "non-responders") depending on their clinical response at Visit 4. Each Placebo sub-group will then be re-randomized to receive either AVP-923 or matching Placebo in a 1:1 ratio.

Patients on Placebo will be considered "responders" if their CGI-S score is between 1 and 3 (inclusive) and their score in the Agitation/Aggression domain in the Neuropsychiatric Inventory (NPI) has decreased by 25% or greater compared to Baseline, at Visit 4 (end of Stage 1). Patients who do not meet these criteria will be considered "non-responders." Assessment of CGI-S and NPI at Visit 4 should be performed, whenever possible, by the same rater who has assessed CGI-S and NPI prior to randomization into Stage 1 of the study.

Patients who received Placebo during Stage 1 and are re-randomized to AVP-923 in Stage 2 will receive AVP-923-20 in the morning and matching Placebo in the evening for the initial 7 days (Stage 2, Days 36-42) of the study. Starting on Day 43, patients will receive AVP-923-20 twice a day for 2 consecutive weeks (Stage 2, Days 43-56) and starting on Day 57, patients will receive AVP-923-30 BID for the remaining 2 weeks (Stage 2, Days 57-70) until study completion.

Those who received Placebo during Stage 1 and are re-randomized to Placebo in Stage 2 will receive Placebo BID throughout Stage 2. Patients who received AVP-923 during Stage 1 are not re-randomized and will continue to take AVP-923-30 for the remaining 5 weeks of the study. All study medication including AVP-923-20 capsules, AVP-923-30 capsules, and Placebo capsules are of identical appearance in order to maintain the integrity of the blind.

3.0 DEFINITION OF STUDY POPULATIONS

3.1 Modified Intent-to-Treat Population

The Modified Intent-to-Treat Population (MITT) will be used for all primary and secondary analyses of efficacy. The MITT population will also be used for some exploratory analyses, to enable meaningful comparisons between the exploratory results and the primary results. Patients will be included in the treatment group to which they were randomized, regardless of treatment received. The MITT population is defined as follows:

- All patients randomized in Stage 1 who had at least one post-Baseline NPI Agitation/Aggression score in Stage 1
- All Placebo non-responders from Stage 1 who are re-randomized in Stage 2 and had at least one post-Week 4 NPI Agitation/Aggression score in Stage 2

3.2 Intent-to-Treat Population

The Intent-to-Treat population (ITT) will include all randomized patients in Stage 1 and Stage 2. The ITT population will be used for some exploratory efficacy analyses.

3.3 Week 4 Evaluable Population

The Week 4 Evaluable Population will be used for exploratory analyses of the primary efficacy parameter and ADCS-CGIC. Patients will be included in the treatment group to which they were randomized, regardless of treatment received. The Week 4 Evaluable Population is defined as follows:

- All patients randomized in Stage 1 who had at least one post-Baseline NPI Agitation/Aggression score in Stage 1 at or following Visit 3
- All Placebo non-responders from Stage 1 who are re-randomized in Stage 2 and had at least one post-Week 4 NPI Agitation/Aggression score in Stage 2 at or following Visit 6

3.4 Safety Population

The safety population (SAF) will be used in the statistical analysis of safety. The SAF population includes all randomized patients who received at least one dose of study treatment. The SAF population will be used for all analyses of safety, and patients will be included in the treatment group based on treatment received.

3.5 Treatment Misallocations

In instances where treatment is improperly allocated to a patient for the entire study, data will be summarized and analyzed as randomized, with the exception of safety data, which will be summarized by actual treatment received.

3.6 Visit Windows

Data at scheduled visits will be assigned to the nominal visit at which the data were collected. The following visit windows in Table 1 are defined to provide derived visits corresponding to

post-Baseline time points for data captured at early termination and unscheduled visits. If two or more visits (nominal and derived) occur within the same analysis window, the latest non-missing assessment will be used. Data from all visits will be presented in the listings.

Table 1: Visit Windows

Stage/Visit	Target Day	Day Range
Stage 1		
Visit 2	8	7-15
Visit 3	22	16-32[1]/day prior to date of Visit 4
Visit 4	36[1]/Date of Stage 2 Study Medication	33[1]-36[1]/Date of Stage 2 Study Medication
Stage 2		
Visit 5	43	Day after date of Stage 2 Study Medication - 53
Visit 6	57	54-67
Visit 7	70	≥ 68

1 For subjects who did not receive Stage 2 study medication

3.7 Change from Baseline Calculation and Missing Data

All analyses will be presented as observed at each scheduled windowed visit (visit windows are defined in Section 3.6). Change from Baseline per stage (as defined for the relevant parameters and visits) at each visit will be calculated for patients with both a Baseline and post-Baseline value at the respective visit as follows:

$$C_{visit\ v} = M_{visitv} - M_{Baseline},$$

where $C_{visit\ v}$ = change in parameter value at post-Baseline visit v,
$M_{visit\ v}$ = the parameter value at post-Baseline visit v, and
$M_{Baseline}$ = the parameter value at Baseline.

If a Baseline value has not been recorded for a parameter, then change from Baseline cannot be calculated for that parameter, and the patient will be excluded from change from Baseline analysis. If a patient discontinues study before the end of a stage the last non-missing post-Baseline observation will be used as the final observation for that stage (LOCF).

If the parameter is related to secondary efficacy (Total NPI, ADCS-ADL, PGI-C, ADCS-CGIC, QoL-AD, CSDD, and CSI [refer to Section 4 and its sub-appendices for details]), the same considerations as stated above hold.

For missing items within questionnaires and scales, please refer to Appendix 2 for imputation rules.

For laboratory, electrocardiogram (ECG), or vital signs parameters, if there are missing values at the target days but there are non-missing values at unscheduled times within the visit windows of the target days, then the unscheduled results will be used as the visit values. For patients who withdraw early, the last non-missing values in either Stage 1 or Stage 2 prior to premature termination will be used as the patient's end-of-study results.

4.0 SCALES AND QUESTIONNAIRE ASSESSMENTS

Refer to Appendix 2 for details on data handling and derivation of scale and questionnaire outcomes.

4.1 Clinical Global Impression of Severity of Illness (CGI-S)

CGI-S is a validated tool used to assess a patient's severity of illness. The assessment is based on a 7-point scale (1-7) where the anchor values are 1 = normal and 7 = among the most extremely ill patients. A value of 0 is given to patients that are not assessed. Patients are assessed at Screening (Day -28 to Day -1), Baseline, Visit 4, Visit 5, and at Visit 7.

The CGI-S Agitation assessment is included as an inclusion criteria requirement. Patients must have a CGI-S Agitation score ≥ 4 (moderately ill) at screening and Baseline to participate in the study.

4.2 Neuropsychiatric Inventory (NPI)

The NPI is a validated clinical instrument for evaluating psychopathology in a variety of disease settings, including dementia. When NPI is not assessed at the center, a nursing home version (NPI-NH) will be used for patients from in-patient or assisted living facilities. The questions in the NPI-NH were rephrased for professional caregivers who may not know the patients prior to the onset of illness; however, the overall instrument domains and scoring are identical to the NPI.

The NPI is a retrospective caregiver-informant interview covering 12 neuropsychiatric symptom domains displayed in Table 2.

Table 2: NPI Domains

A: Delusions	G: Apathy/indifference
B: Hallucinations	H: Disinhibition
C: Agitation/Aggression	I: Irritability/Lability
D: Depression/Dysphoria	J: Aberrant motor behavior
E: Anxiety	K: Sleep/Nighttime behavior disorders
F: Euphoria/elation	L: Appetite/Eating changes

Neuropsychiatric manifestations within a domain are collectively rated by the caregiver in terms of both frequency (1 = Occasionally, less than once per week, to 4 = Very frequently, once or more per day) and severity (1 = Mild to 3 = Marked), yielding a composite symptom domain score.

Domain Score = Frequency x Severity

For a given NPI domain, a potential assessed domain score has a range from 1 to 12. A total overall NPI score is calculated by summing the NPI domain scores for all 12 domains (A through L) together.

Caregiver distress is rated for each positive neuropsychiatric symptom domain on a scale ranging from 0 (Not at all) to 5 (Very severely or extremely). The total caregiver distress score is generated by adding together the scores of all 12 domains of the NPI distress questions. Scores range from 0 to 60 with the higher score indicating extreme distress.

The NPI is administered to the patient's caregiver at Baseline, Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, and Visit 7. At Baseline, Visit 4, and Visit 7, the NPI will be used to evaluate behaviors within the past 4 weeks. At other visits, behaviors will be evaluated from last visit.

The Agitation/Aggression domain in the NPI is the primary efficacy endpoint – see Section 5.4.1.

Note that responders are defined as having a 25% or greater reduction from Baseline to Visit 4 in the Agitation/Aggression domain, in combination with a Visit 4 CGI-S Agitation score of 1, 2, or 3. This will be used to determine response status ("Responder" or "Non-Responder") for Stage 1 treatment (patients on Placebo).

4.3 Mini-Mental State Examination (MMSE)

The MMSE is a brief test that is used to screen for cognitive impairment. The MMSE scale comprises 11 questions or simple tasks concerning orientation, memory, attention, and language to evaluate the patient's cognitive state. The anchor values are not consistent for each task (refer to Table 3). The MMSE total score is calculated by summing the item scores across all 11 tasks. A patient's total possible MMSE score ranges from 0 to 30 points. Higher scores indicate milder cognitive impairment.

At Stage 1 randomization, both CGI-S (severity of agitation – moderate vs. severe) and screening MMSE assessments (cognitive function – high vs. low) are used as stratification factors.

The MMSE assessment is included as an inclusion criteria requirement. Patients must have a MMSE score between 8 and 28 (inclusive) for study entry. The MMSE is assessed at Screening (Day -28 to Day -1), Visit 4, and Visit 7.

Table 3: Mini-Mental State Examination (MMSE)

Item	Score Range
Orientation to Time	0 to 5
Orientation to Place	0 to 5
Registration	0 to 3
Attention and Calculation	0 to 5
Recall	0 to 3
Naming	0 to 2
Repetition	0 to 1
Comprehension	0 to 3
Reading	0 to 1
Writing	0 to 1
Drawing	0 to 1

4.4 Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (ADCS-ADL)

The ADCS-ADL inventory measures basic activities of daily living such as dressing, conversation, eating, bathing, and grooming. The 19-item version, covering mainly basic ADL, is used for the assessment of patients with more severe disabilities. ADCS-ADL uses a scale from 0 to 54, with lower scores indicating declining ability. The ADCS-ADL is assessed at Baseline, Visit 4, and Visit 7.

4.5 Cornell Scale for Depression in Dementia (CSDD)

The CSDD was specifically developed to assess signs and symptoms of major depression in patients with dementia. Because some of these patients may give unreliable reports, the CSDD uses a comprehensive interviewing approach that derives information from the patient and the informant. Information is elicited through two semi-structured interviews: an interview with an informant and an interview with the patient. The interviews focus on depressive symptoms and signs occurring during the week preceding the assessment.

The CSDD has 19 items, and each item is rated for severity on a scale of 0-2 (0 = absent, 1 = mild or intermittent, 2 = severe). The item scores are added. Scores above 10 indicate a probable major depression. Scores above 18 indicate a definite major depression. Scores below 6 as a rule are associated with absence of significant depressive symptoms.

The CSDD is assessed at Screening (Day -28 to Day -1), Visit 4, and Visit 7.

4.6 Caregiver Strain Index (CSI)

The CSI is a tool that can be used to quickly identify families with potential caregiving concerns. It is a 13-question tool that measures strain related to care provision. There is at least one item for each of the following major domains: Employment, Financial, Physical, Social, and Time. Positive responses to 7 or more items on the index indicate a greater level of strain. A 0 (No) to 1 (Yes) scale is used for each of the 13 questions. The CSI is assessed at Baseline (Day 1), Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, and Visit 7.

4.7 Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-cog)

The ADAS was designed to evaluate the cognitive and non-cognitive behavioral dysfunction characteristics of patients with AD. The cognitive sub-scale (ADAS-cog) consists of 10 tasks related to memory, praxis, and language. Scoring for each component of the ADAS-cog is as follows:

- Word Recall Task: Mean number of words not recalled on three trials (maximum score = 10)
- Naming Task: Number of objects named incorrectly, ranging from 0 (0-2 items) to 5 (15-17 items)
- Commands: Number of correct and incorrect commands, ranging from 0 (all commands correct) to 5 (all 5 commands incorrect)
- Constructional Praxis: Number of drawings correct, ranging from 0 (all 4 drawings correct) to 5 (no figures drawn, no recognizable attempt at drawing any side/section of any figure)

- Ideational Praxis: Number of components performed correctly, ranging from 0 (all components performed correctly) to 5 (failure to perform 5 components)
- Orientation: One point given for each incorrect response (maximum = 8)
- Word Recognition: Mean number of words not recognized on 3 trials (maximum error score = 12)
- Remembering Test Instructions: Subject's ability to remember the requirements of the Word Recognition Task, ranging from 0 (subject never needs extra reminders of instructions) to 5 (severe – must be reminded 7 or more times)
- Spoken Language Ability: Subject's quality of speech, ranging from 0 (no instances when it is difficult to understand the subject) to 5 (severe – 1- or 2-word utterance; fluent but empty speech; mute)
- Word-finding Difficulty: Subject's ability in expressive language, ranging from 0 (no evidence) to 5 (severe – nearly total loss of content words; speech sound empty; 1- to 2-word utterances)
- Comprehension of spoken language: Subject's ability to understand what is being said to them, ranging from 0 (patient understands) to 5 (severe – patient rarely responds to questions appropriately; not due to poverty of speech)

The ADAS-cog is assessed at Baseline, Visit 4, and Visit 7. The total ADAS-cog score ranges from 0 to 70 where higher scores indicate greater cognitive impairment.

4.8 Patient Global Impression of Change (PGI-C)

The PGI-C is single judgment based on a 7-point (1-7) scale used to assess treatment response, and it is rated as: 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse), or 7 (very much worse).

In this study, PGI-C will be assessed and rated by the patient's caregiver at Visit 4 and Visit 7 and will focus on the patient's agitation. At both visits, the PGI-C will assess change from the Baseline (Day 1) visit.

4.9 Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change Rating (ADCS-CGIC)

The intent of the ADCS version of the Clinical Global CGIC is to provide a means to reliably assess global change from Baseline in a clinical trial. It provides a semi-structured format to allow clinicians to gather necessary clinical information from both the patient and caregiver, in order to make a global impression of clinical change. ADCS-CGIC is rated as: marked improvement, moderate improvement, minimal improvement, no change, minimal worsening, moderate worsening, or marked worsening.

The standard ADCS-CGIC instrument was modified to better assess aspects relevant to studying agitation in AD. The modified version contains additional questions related to agitation and an additional assessment of the Clinician's Impression of Change focused specifically on agitation.

This modified version of the ADCS-CGIC was originally designed for the Citalopram study for Agitation in Alzheimer's disease (CitAD[9]) and is used with permission from the study group.

In this study, a Baseline ADCS-CGIC evaluation will be conducted, and then the modified ADCS-CGIC will be assessed at Visit 4 and Visit 7 for both Agitation and Overall Clinical Status. At Visit 4, the ADCS-CGIC will be completed to assess change from the Baseline (Day 1) visit. At Visit 7, the ADCS-CGIC will be completed to assess change from Visit 4 and change from the Baseline (Day 1) visit.

The ADCS-CGIC from Visit 4 to Visit 7 will be performed retrospectively for all patients who completed Visit 7 prior to Amendment 3, based on the existing ADCS-CGIC evaluation worksheets that allow the clinician to record assessments of clinical severity and of change over time.

4.10 Quality of Life-Alzheimer's Disease Measure (QoL-AD)

The QoL-AD is a brief, 13-item measure designed specifically to obtain a rating of the patient's quality of life from both the patient and the caregiver. It was developed for individuals with dementia, based on patient, caregiver, and expert input, to maximize construct validity, and to ensure that the measure focuses on QoL domains thought to be important in cognitively impaired older adults. It uses simple and straightforward language and responses and includes assessments of the individual's relationships with friends and family, concerns about finances, physical condition, mood, and an overall assessment of life quality. Caregivers complete the measure as a questionnaire about their patients' QoL, while patients complete it in interview format about their own QoL. The measure consists of 13 items, rated on a 4-point scale, with 1 being poor and 4 being excellent. Total scores range from 13 to 52, with higher score indicating better QoL. The QoL-AD is assessed at Baseline, Visit 4, and Visit 7.

5.0 STATISTICAL ANALYSIS METHODS

5.1 Patient Disposition and Patient Status

Patient status will provide a global summary of the numbers of patients randomized to Placebo or AVP-923 and treated during Stage 1, the numbers in each treatment group who discontinued during Stage 1, the numbers re-randomized into Placebo or AVP-923 (either new to AVP-923 or continuing) and treated during Stage 2 by responder status, the numbers who discontinued during Stage 2 by treatment and responder status, and the numbers completing both stages of the study.

Final patient disposition will be summarized by the number of patients who completed a study stage, the primary reason for discontinuation, and the stage at which the patient discontinued. Patient Disposition and Patient Status will be tabulated for the MITT, ITT, and SAF populations using counts and percentages. Percentages will be determined using the counts of patients available for each population appropriate to Stage and treatment.

A supporting listing of patient disposition at the end of the study will also be provided.

5.2 Demographic Characteristics

Demographic characteristics will be summarized using number and percent for categorical variables and descriptive statistics (n, mean, standard deviation (SD), minimum, median,

maximum) for quantifiable variables. Since these summaries display data collected once, at the start of the study, the tables will display the groups to which the patients were originally randomized, as well as an overall column, for both the ITT and MITT populations. Demographic characteristics will also be summarized for all patients entering Stage 2 (by Stage 2 treatment group) and for Stage 1 Placebo non-responders re-randomized in Stage 2 (by Stage 2 treatment group). The variables to be summarized can be found in Table 4 below. For each categorical parameter, the denominator for the percentages will be the number of patients who had that parameter assessed. A supporting listing of patient demographics will also be provided.

Table 4: Demographic Characteristics

Characteristic	Summarized as:	Categories
Gender	Categorical	• Female • Male
Race	Categorical	• White • Black or African American • Asian • American Indian or Alaska Native • Native Hawaiian or Other Pacific Islander • Other
Ethnicity	Categorical	• Hispanic or Latino • Not Hispanic or Latino
Age/Age group (years)	Continuous and Categorical	Age Group: • < 75 • ≥ 75
Patient Living Arrangements	Categorical	• Outpatient • Assisted living • Nursing home
CGI-S Agitation Score	Continuous	
Metabolizer Status based on CYP2D6 genotype	Categorical	• Poor metabolizers • Intermediate metabolizers • Extensive metabolizers • Ultra-rapid metabolizers

5.3 Treatment Compliance

Study medication will be dispensed on Days 1, 8, 22, 36, 43, and 57 (Baseline to Visit 6). Patients will be considered compliant if at least 80% of their scheduled doses are taken. Overall compliance with the dosing regimen will be defined as the ratio of study medication taken to the expected amount of study medication taken.

$$Treatment\ Compliance = 100\ x\ \frac{Amount\ of\ Study\ Medication\ Taken}{Expected\ Amount\ of\ Study\ Medication\ Taken}$$

When calculating overall treatment compliance, the overall number of days on study drug (last dose day – first dose day + 1) will be considered in determining the expected amount of study

medication taken. If a patient does not return any of their medication, the site will be queried to confirm the number of doses taken by the patient, based upon the returned source diary.

5.4 Primary Efficacy Analysis

All efficacy analyses are described in Appendix 4.

5.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is based on both stages of the study; in Stage 1, it will assess the change in score of the Agitation/Aggression domain of the NPI from Baseline to Visit 4 and, in Stage 2, the change from Visit 4 (Stage 2 Baseline) to Visit 7.

Baseline for Stage 1 is the NPI value at Day 1. Placebo patients who are assessed as non-responders at Visit 4 and re-randomized to either continued Placebo or AVP-923 will have their Visit 4 value used as the Baseline for Stage 2.

5.4.2 Primary Efficacy Statistical Methods

The primary efficacy analysis will be based on a Sequential Parallel Comparison Design (SPCD) in which data from the 2 Stages are analyzed together using the MITT population. The method is described in detail by Chen et al[1]. The Ordinary Least Squares (OLS) analysis method will be used.

At the end of each Stage, an Analysis of Covariance (ANCOVA) model will be applied using data from that Stage to test the null hypothesis that the change due to Placebo is equal to that due to AVP-923 versus the alternative that there is a difference between treatments. Stage 1 will include all patients randomized to Placebo or AVP-923 who had data at Baseline and at least one post-Baseline visit during Stage 1. Stage 2 will consist only of data from patients randomized to Placebo at Stage 1 who completed the stage, were evaluated as "non-responders" according to pre-determined criteria, and were re-randomized to either Placebo or AVP-923.

The model will be:

$$C_{Stagei} = \alpha^{(i)} + \beta^{(i)} * Baseline_i + \theta^{(i)} * Treatment + error,$$

where C_{Stagei} = change from Baseline to end of Stage i, where i = 1, 2,
$Baseline_i$ = Stage $_i$ Baseline value at Stage i, i = 1, 2, and
Treatment = treatment AVP-923 indicator during Stage i, where i = 1, 2 (value = 1 if subject assigned to AVP-923 during Stage i and 0 if patient assigned to Placebo)

From the individual Stage analyses, the treatment effect estimates $\theta^{(i)}$ (change due to AVP-923 - change due to Placebo) at Stage i and variances of the treatment effects estimates $Var(\theta^{(i)})$ at Stage i are included as part of the output. Then, using predetermined weights for each Stage (in this study the weights are $w = w_i = 0.5$, for i = 1, 2), the values are used to construct a weighted OLS statistic to test the null hypothesis that the treatment effect among patients in Stage 1 and the treatment effect among Placebo non-responders in Stage 2 are equal to 0.

The test statistic is calculated as:

$$Z_{OLS} = (w\theta^{(1)} + (1-w)\theta^{(2)}) / \text{SQRT}\ (w^2\text{Var}(\theta^{(1)}) + (1-w)^2\ \text{Var}(\theta^{(2)})),$$

Under the null hypothesis, the observed value is compared against a normal critical value of 1.96 (corresponding to a two-sided test at the alpha = 0.05 level of significance). Chen et al.[1] showed that such a procedure preserves the type I error.

5.5 Secondary Efficacy Analyses

The following secondary efficacy analyses will be carried out using the MITT population.

5.5.1 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7 in the total NPI
- Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7 in all other domains of the NPI, separately
- Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7 in the sum of the following NPI domains: Agitation/Aggression (C), irritability/lability (I), disinhibition (H), and aberrant motor behaviors (J) – herein called 'NPI4D' – a cluster of neuropsychiatric manifestations common in patients with agitation which also approximates the scope of behaviors assessed by the Cohen Mansfield Agitation Inventory (CMAI) and Neurobehavioral Rating Scale-agitation subscale (NBRS-A) scales[7, 8]
- Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7 in the sum of the following NPI domains: Agitation/Aggression (C), irritability/lability (I), anxiety (E), and aberrant motor behaviors (J) – herein called 'NPI4A'
- Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7 in the NPI Caregiver Distress Score for the NPI Agitation/Aggression Domain
- Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7 in the NPI Caregiver Distress Score for Total NPI
- Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7 in the NPI Caregiver Distress Score for NPI4D
- Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7 in the NPI Caregiver Distress Score for NPI4A
- Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7 in the ADCS-ADL
- Change from Stage 1 Baseline to Visits 2 and 3, and change from Stage 2 Baseline to Visits 5 and 6 in the Agitation/Aggression domain of the NPI
- Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7 in the QoL-AD
- Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7 in the CSDD

- Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7 in the CSI
- Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7 in the MMSE
- ADCS-CGIC Agitation at Visit 4 and Visit 7 relative to change from Stage 1 Baseline
- ADCS-CGIC Agitation at Visit 7 relative to change from Visit 4
- ADCS-CGIC Overall Clinical Status at Visit 4 and Visit 7 relative to change from Stage 1 Baseline
- ADCS-CGIC Overall Clinical Status at Visit 7 relative to change from Visit 4
- PGI-C (rated by a caregiver) at Visit 4 and Visit 7

Per protocol, the same methodology used for the analysis of the primary endpoint will be used for these secondary endpoints, making adjustment to study weeks being compared as appropriate. For the analyses of ADCS-CGIC and PGI-C, ANOVA will be used instead of ANCOVA, as there is no Baseline assessment.

- Change from Stage 2 Baseline to Visits 5 and 6 in the Agitation/Aggression domain of the NPI

This analysis will be completed using an ANCOVA model with treatment as a factor and the Baseline value as a covariate.

5.5.2 Other Secondary Endpoints

Changes in the use of concomitant psychotropic drugs - the concomitant use of psychotropic drugs is allowed. These drugs include:

> donepezil, rivastigmine, galantamine, memantine, citalopram, escitalopram, fluvoxamine, fluoxetine, sertraline, paroxetine, venlafaxine, develafaxine, duloxetine, milnacipram, midazolam, oxazepam, brotizolam, triazolam, alprazolam, trazodone, eszopiclone, zopiclone, zolpidem, zaleplon, apiprazole, asenapine maleate, clozapine, iloperidone, lurasidone, olanzapine, olanzapine/fluoxetine, paliperidone, quetiapine, risperidone, ziprasidone, butyrophenones, buspirone, lorazepam

Changes in the use of these drugs from Baseline use, eg, increases/decreases in dose, changes in frequency, addition/discontinuation, will be summarized. Patients may be counted in multiple categories of change.

Patients are allowed to receive oral lorazepam as rescue medication for the short-term treatment of symptoms of agitation if deemed necessary by the investigator. Lorazepam can be administered in a dose up to 1.5 mg/day and should not exceed 3 days in a 7-day period. A summary of the use of lorazepam as rescue medication, by visit, will be provided, along with a patient listing.

5.6 Exploratory Analyses

Exploratory efficacy analyses will be carried out using the ITT population, MITT population, or Week 4 Evaluable population, as appropriate. For each exploratory analysis below, the population to be used will be indicated. For patients receiving Placebo at Stage 1 and AVP-923 at Stage 2, Stage 1 Baseline is defined as the last non-missing assessment prior to Stage 1 randomization for assessments during Stage 1 and Stage 2 Baseline is defined as the last non-missing assessment prior to Stage 2 re-randomization for assessments during Stage 2.

5.6.1 Analysis of ADAS-cog

This exploratory analysis will be carried out using the ITT population.

Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7 in the total ADAS-cog will be performed using the same statistical methodology as described in Section 5.4.2 for the primary analysis.

5.6.2 Sensitivity Analysis of the Primary Efficacy Endpoint

This exploratory analysis will be carried out using the ITT population and the MITT population.

An exploratory sensitivity analysis of the primary efficacy endpoint will be conducted using the repeated measures model described by Doros et al. (2013).[6] This model uses all available data for the NPI Agitation/Aggression domain, ie, Baseline plus the 3 visits from each of the 2 stages. Three separate models are used to estimate the treatment effect using data collected at Baseline, end of Stage 1, and end of Stage 2, with a general model that allows the data from intermediate visits to be part of the analysis (see Section 2.4 of the Doros et al. paper).

In this analysis, the unstructured covariance model will be used. However, if there are convergence problems, the use of the first-order autoregressive (AR1) and/or the compound symmetry (CS) covariance structures will be considered.

In addition, the following comparisons will be carried out for the primary endpoint and for Total NPI , NPI4A, and NPI4D, using the MITT population:

- exclude patients who did not use the same version of the NPI throughout the study (patients who used the NPI-NH at one or more visits and the NPI version at other visits), and
- exclude patients who used the NPI-NH version (rather than the NPI version) throughout the study.

These exploratory analyses will be carried out using the primary statistical analysis described in Section 5.4.2.

5.6.3 Additional Analyses of Efficacy Endpoints

The following exploratory analyses will be carried out using the MITT population.

In this exploratory analysis, the following alternative definition of a "Responder" will be considered:

- 25% or greater reduction from Baseline to Day 36 (Visit 4) in the NPI Agitation/Aggression domain

For the above definition, the primary statistical analysis described in Section 5.4.2, and the secondary analyses described in Section 5.5.1 will be repeated. This alternative definition will likely result in a different group of patients included in the analysis, since Stage 2 data are only incorporated for Placebo non-responders at Stage 1.

In addition, the primary statistical analysis described in Section 5.4.2 and the secondary analyses described in Section 5.5.1 will be applied to a comparison including Placebo responders in Stage 1 as well as non-responders.

The following exploratory analyses will be carried out using the Week 4 Evaluable population:

- Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7 in the Agitation/Aggression domain of the NPI
- ADCS-CGIC Agitation at Visit 4 and Visit 7 related to change from Stage 1 Baseline
- ADCS-CGIC Agitation at Visit 7 related to change from Visit 4

The primary statistical analysis described in Section 5.4.2 will be used for the analysis of NPI Agitation/Aggression change from Baseline and the same methodology as defined in Section 5.5.1 will be used for the analysis of ADCS-CGIC.

The following exploratory analysis will be carried out using the MITT population:

- Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7 in the NPI Caregiver Distress Score

In addition, for ADCS-CGIC Agitation and PGI-C, to capitalize on the ordered categories of each rating scale, proportional odds regression will be used to compare responses between treatments at each visit using the MITT population. A treatment effect estimate will be generated as the Odds Ratio of being at or better than a given category for AVP-923 versus Placebo. A treatment effect estimate greater than 1.0 favors AVP-923. The SPCD design will be maintained as the results at Visit 7 will include only the Stage 1 Placebo non-responders re-randomized in Stage 2.

5.6.4 Comparisons Between Additional Patient Groupings

Additional data groupings will be defined as described below and in Figure 1:

- A: Stage 1 data for patients randomized to Placebo in Stage 1
- B: Stage 1 data for patients randomized to AVP-923 in Stage 1
- C: Stage 2 data for Placebo non-responders in Stage 1 who are randomized to Placebo in Stage 2
- D: Stage 2 data for Placebo non-responders in Stage 1 who are randomized to AVP-923 in Stage 2
- E: Stage 2 data for Placebo responders in Stage 1 who are randomized to Placebo in Stage 2
- F: Stage 2 data for Placebo responders in Stage 1 who are randomized to AVP-923 in Stage 2
- G: Stage 2 data for AVP-923 patients in Stage 1 who continue on AVP-923 in Stage 2

The following comparison will be tested for the primary endpoint and for NPI4A and NPI4D using the MITT population:

- Change from Stage 1 Baseline to Visit 4 comparing data for patients randomized to AVP-923 in Stage 1 (A from Figure 1) to data for patients randomized to Placebo in Stage 1 (B from Figure 1)

This analysis will be completed using an ANCOVA model with treatment as a factor and the Stage 1 Baseline value as a covariate.

The following comparisons will be carried for the primary endpoint and for Total NPI , NPI4A, and NPI4D using the MITT population:

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- Number (%) of patients with >=25% decrease at Visit 4 from Stage 1 Baseline, >=50% decrease at Visit 4 from Stage 1 Baseline, and >=75% decrease at Visit 4 from Stage 1 Baseline for patients in the Only Placebo group (A plus C plus E from Figure 1) vs patients in the Only AVP-923 group (B plus G from Figure 1)

- Number (%) of patients with >=25% decrease at Visit 7 from Stage 2 Baseline, >=50% decrease at Visit 7 from Stage 2 Baseline, and >=75% decrease at Visit 7 from Stage 2 Baseline for Stage 1 Placebo patients re-randomized to Placebo in Stage 2 (C plus E from Figure 1) vs Stage 1 Placebo patients re-randomized to AVP-923 in Stage 2 (D plus F from Figure 1)

The following exploratory analyses will be carried out using the ITT population.

The following comparison will be tested for the primary and secondary efficacy endpoints, making adjustment to study weeks being compared as appropriate:

- Change from Baseline to Visit 7/LOCF comparing data for patients randomized to AVP-923 in Stage 1 (B plus G from Figure 1) to data for patients randomized to Placebo in Stage 1 who also received Placebo in Stage 2 (A plus C plus E from Figure 1)

This analysis will be completed using an ANCOVA model with treatment as a factor and the Stage 1 Baseline value as a covariate.

A longitudinal analysis of the NPI Agitation/Aggression domain scores using data from all visits (Baseline, Visits 1 through 7) will also be performed. This analysis will compare treatment groups over time using a linear mixed effects model with random intercept and slope for each patient. This analysis will be done comparing patients who received only Placebo (A plus C plus E from Figure 1) versus patients who received only AVP-923 (B plus G from Figure 1). The same analysis will be performed for the key secondary efficacy parameters that are collected at multiple visits (beyond just Baseline, Visit 4, and Visit 7) - total NPI, NPI4D, NPI4A, all other domains of the NPI separately, and CSI.

5.6.5 Subset Analyses Based on Stage 1 Baseline Responses

The following patient subset of the ITT population, based on the results of the CiTAD study[9], will be constructed based on Stage 1 Baseline:

- NPI Agitation/Aggression domain frequency score = 4 or (NPI Agitation/Aggression domain frequency score ≥ 3 and NPI Agitation/Aggression domain severity score ≥ 2)

The primary statistical analysis described in Section 5.4.2 will be applied for the primary and secondary efficacy endpoints for the ITT patient subset defined above.

- Descriptive statistics (n, mean, standard deviation (SD), minimum, median, maximum) will be calculated for the following efficacy parameters using the MITT population, for patients with CGI-S Agitation scores of 4 vs. >4 at Stage 1 Baseline: Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7 in the Agitation/Aggression domain of the NPI
- Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7 in the NPI4D
- Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7 in the NPI4A

5.7 Safety Analysis

5.7.1 Safety Endpoints

Safety will be assessed by the following:

- Adverse Events (AEs)
- Physical and Neurological examination
- Vital Signs
- Clinical laboratory values such as serum biochemistry, hematology, and urinalysis
- Resting 12-lead ECG
- Study discontinuation due to an adverse event or lack of efficacy

For patients only receiving AVP-923, Baseline is defined as the last non-missing assessment prior to Stage 1 randomization. Otherwise, for non-responders receiving Placebo at Stage 1 and re-randomized into Stage 2, Baseline is defined as the last non-missing assessment prior to Stage 1 randomization for assessments during Stage 1 and the last non-missing assessment prior to Stage 2 re-randomization for assessments during Stage 2.

In general, safety will be summarized by Only Placebo, Only AVP-923 and Placebo/AVP-923. Patients who received only Placebo or AVP-923 will be summarized as Only Placebo or Only AVP-923, respectively. Patients randomized to Placebo at Stage 1 and then re-randomized to AVP-923 at Stage 2 are summarized as Placebo/AVP-923. Safety data will also be summarized by All Placebo or All AVP-923. All Placebo and All AVP-923 are defined as patients receiving study medication (Placebo or AVP-923, respectively) at either Stage.

5.7.2 Statistical Methods for Safety Analysis

5.7.2.1 Adverse Events (AEs)

AE summaries will be reported on the Safety Population. Medical Dictionary for Regulatory Activities (MedDRA) version 16.0 will be used to code AEs.

Treatment-emergent adverse events (TEAEs) are defined as adverse events which first occur, or worsen, after the first dose of study medication and within 30 days after the permanent discontinuation of the study medication (first dose date ≤ AE start date ≤ date of last dose + 30 days).

Key guidelines for counting the number and percent of patients with adverse events are as follows.

- When a patient has the same AE reported multiple times during an analysis period based on preferred terminology [System Organ Class (SOC), Preferred Term (PT)], the patient will only be counted once within a level of MedDRA. If a patient in the Placebo/AVP-923 group has an AE with onset during Stage 1 (while on Placebo) that continues into Stage 2 (while on AVP-923), as long as there is no increase in severity, the AE will be counted only for Placebo. If the AE increases in severity or has a new occurrence in Stage 2, it will also be counted for AVP-923.

- When assessing investigator reported relationship to study drug of the AEs, if an AE changes in causal relationship for a patient, the most related event will be chosen. Related AEs will include those reported as probably or possibly related by the investigator and those with a missing relationship.

- When assessing severity of the AEs, if an AE changes in severity (mild < moderate < severe) during an analysis period for a patient, the AE with the worst severity will be chosen. An AE with a missing severity will be excluded from summaries of intensity.

- When assessing severity for drug-related AEs as reported by the investigator, only drug-related AEs (possible, probably, and missing relationship) will be used in the analysis. If a patient has the same AE reported multiple times during an analysis period for a drug-related AE, the AE with the worst severity will be chosen. An AE with a missing severity will be excluded from summaries of intensity.

- Patients who prematurely discontinue at either stage and experience an AE within 30 days of final dose will have that AE counted for the treatment being taken during the stage at which discontinuation occurs.

All AE data will be presented in data listings which include both the stage/treatment group in which the AE occurred and the randomized treatment received.

In general, TEAE tables will be summarized by each treatment group (Only Placebo, Only AVP-923 and Placebo/AVP-923, All Placebo, All AVP-923) defined in Appendix 3. For summaries by dose and age group, TEAEs will be summarized by All Placebo and All AVP-923; for summaries of duration and recurrence, and time to onset, TEAEs will be summarized by Only Placebo and Only AVP-923.

In summaries by SOC and PT, the SOCs will be presented in alphabetical order, and the PTs will be presented by descending frequency in the All AVP-923 group and then alphabetically within each SOC. In summaries by PT, the PTs will be presented in decreasing frequency based on the overall AVP-923 group.

Refer to Appendix 5 for details of imputing partial Start Dates of Adverse Events.

5.7.2.1.1 Overview of Adverse Events

The number and percent of patients experiencing AEs will be summarized for the following AE categories:

- Overall AEs (All AEs and TEAEs)
- Patients with at least one TEAE, drug-related TEAE, Serious TEAE, and drug-related Serious TEAE
- Patients who discontinued treatment due to TEAE, drug-related TEAE, Serious TEAE, and drug-related Serious TEAE
- Overall deaths (for any reason)
- Deaths due to drug-related TEAE

5.7.2.1.2. All Treatment Emergent Adverse Events

The following summaries for all TEAEs will display the number and percent of patients for each group (Only Placebo, Only AVP-923, Placebo/AVP-923, All Placebo, All AVP-923) defined above:

- TEAEs by SOC and PT
- TEAEs by SOC and PT by maximum severity
- TEAEs by PT

The following will be summarized by All Placebo and All AVP-923 treatment groups:

- TEAEs by SOC, PT, and dose
- TEAEs by SOC, PT, and age group

5.7.2.1.3. Serious Treatment Emergent Adverse Events

The following summaries will display the number and percent of patients with serious TEAEs by SOC and PT for each group (Only Placebo, Only AVP-923, Placebo/AVP-923, All Placebo, All AVP-923) defined above:

- All serious TEAEs
- Drug-related serious TEAEs
- Serious TEAEs leading to discontinuation of study drug

All serious AEs (treatment-emergent and non-treatment-emergent) will be listed.

5.7.2.1.4. Related Treatment Emergent Adverse Events

Related TEAEs will include those reported as probably or possibly related to study drug as assessed by the investigator and those with a missing relationship. The number and percent of patients with related TEAEs will be summarized by SOC and PT, and by SOC, PT, and maximum severity for each group (Only Placebo, Only AVP-923, Placebo/AVP-923, All Placebo, All AVP-923) defined above. In addition, the number and percent of patients with serious related TEAEs will be summarized by PT for each treatment group.

The following summaries will also be done for the Only Placebo and Only AVP-923 treatment groups:

- Time (days) to first onset of common treatment-related TEAEs
- Duration (days), percentage of total study days, and recurrence of common treatment-related TEAEs
- Time to discontinuation due to treatment-related TEAEs

Common TEAEs are defined as TEAEs with PT = nausea, dizziness, somnolence, agitation, aggression, diarrhea, fall, fatigue, headache, or any other TEAE with an incidence of > = 3% in the Only AVP-923 treatment group and > = 2 times the incidence in the Only Placebo treatment group.

For the time to first onset summary, a Kaplan-Meier approach will be used where patients who do not have the event of interest will be right-censored at the time of their final visit.

Duration is defined as the number of days for the longest occurrence of the event (if experienced more than once); percentage of total study days is defined as total duration of event (sum of durations of same related TEAE) divided by the total study days completed by the patient x 100; recurrence is defined as a new report of the same related TEAE with a new start and stop date.

5.7.2.1.5. Deaths

Any patient deaths during the course of this study will be included in the Overview of Adverse Events, Reasons for Discontinuation in the Study Disposition table and in by-patient data listings.

5.7.3 Physical and Neurological Examination

Physical and Neurological examinations are assessed at Screening (Day -28 to Day -1), Visit 4, and Visit 7.

A shift in assessment tabulation from Baseline to Final Visit will be presented. Baseline will be defined as the last assessment prior to receiving study medication. For patients receiving Placebo during Stage 1 and re-randomized to AVP-923 at Stage 2, Baseline will be defined as last assessment prior to re-randomization and summarized as AVP-923. The counts and percentages of each Baseline and Final Visit tabulation will be based on the number of patients with both a Baseline and Final Visit value. The denominator used to calculate the percentages will be based on the Baseline assessment (Normal, Abnormal) totals.

5.7.4 Vital Signs

Systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and body temperature will be summarized by treatment (Only Placebo, Only AVP-923, Placebo/AVP-923, All Placebo, All AVP-923) with descriptive statistics (mean, standard deviation, minimum, median, and maximum) for the average Baseline value, average actual value, average change from Baseline value, and average percent change from Baseline value to each post-Baseline visit and Final Visit. The change from Baseline tabulations will only be performed on patients with both a Baseline and post-Baseline measurement. Refer to Appendix 3 Treatment Group Rationale by Table Type, for guidance on how the summaries will be displayed.

The number and percentage of patients who meet potentially clinically significant (PCS) criteria for Systolic BP, Diastolic BP, and Pulse Rate will be presented by Stage for each treatment group based on Any Visit during the Stage. The PCS criteria are presented in the Table 5 below:

Table 5: Vital Signs PCS Criteria

Vital Signs Parameter	Increases	Decreases
SBP	> 180 mmHg AND ≥ 20 mmHg increase from Baseline	<= 90 mmHg AND >= 20 mmHg decrease from Baseline
DBP	≥ 105 mmHg AND ≥ 15 mmHg increase from Baseline	<= 50 mmHg AND >= 15 mmHg decrease from Baseline
Pulse Rate	≥ 120 bpm AND ≥ 15 bpm increase from Baseline	<= 50 bpm AND >= 15 bpm decrease from Baseline
SBP and Pulse Rate	Increase from Baseline of ≥ 10 mmHg for SBP and ≥ 5 bpm for Pulse Rate	N/A
DBP and Pulse Rate	Increase from Baseline of ≥ 5 mmHg for DBP and ≥ 5 bpm for Pulse Rate	N/A

5.7.5 Clinical Laboratory Parameters

Hematology, Blood Chemistry, and Urinalysis laboratory safety parameters will be assessed at Screening (Days -28 through -1) and at Visits 4 and 7. The complete list of tests in each category can be found in Section 6.3.4 of the study protocol.

At each time point, for each treatment group, quantitative variables will be summarized by n, mean, standard deviation, minimum, median, and maximum. The International System of Units (SI units) will be used for these laboratory summaries.

Changes from Baseline will be calculated at Visits 4 and 7 and summarized using the same summary statistics. Refer to Appendix 3 Treatment Group Rationale by Table Type for details on treatment-group displays of the summary values.

Shift tables, relating Baseline to post-Baseline results with respect to normal limits for each test, will be generated by treatment. A shift in assessment tabulation from Baseline to post-Baseline will be presented. Baseline will be defined as the last assessment prior to receiving study medication. For patients receiving Placebo during Stage 1 and re-randomized to AVP-923 at Stage 2, Baseline will be defined as last assessment prior to re-randomization and summarized as AVP-923. The counts and percentages of each Baseline and post-Baseline tabulation will be based on the number of patients with both a Baseline and post-Baseline value. The denominator

used to calculate the percentages will be based on the Baseline assessment totals Laboratory tests without normal limits will not have shift tables produced.

The number and percentage of patients who meet potentially clinically significant (PCS) criteria for selected laboratory tests will be presented by Stage for each treatment group based on any visit during the stage. The PCS criteria are presented in the Table 6 below:

Table 6: Potentially Clinically Significant Abnormal Laboratory Values

Potentially Clinically Significant (PCS) Laboratory Criteria			
		PCS Criteria	
Laboratory Parameter	**Unit**	**Low PCS Criteria**	**High PCS Criteria**
Hematology			
Hemoglobin	g/dL	< 10	> 18
Hematocrit	%	< 30	> 50
Platelet Count	x10^3/uL	≤ 75	≥ 700
Leukocyte (White Blood Cell Count)	x10^3/uL	≤ 2.8	≥ 16
Eosinophils	%	No lower limit	≥ 10
Neutrophils	%	≤ 15	No upper limit
Erythrocyte (Red Blood Cell Count)	x10^6/uL	≤ 2.5	≥ 7.0
Basophils		NA	> 300/3mm
Lymphocytes		≤ 500/3mm	> 4000/3mm
Monocytes		NA	> 1000/3mm
Bands		NA	NA
Morphology		NA	NA
Chemistry			
ALT (SGPT)	U/L	No lower limit	≥ 3 X ULN
AST (SGOT)	U/L	No lower limit	≥ 3X ULN
Total Bilirubin	mg/dL	No lower limit	≥ 1.5 ULN
BUN	mg/dL	No lower limit	≥ 30.0
Creatinine Kinase (CK)	U/L	No lower limit	≥ 3 ULN
Sodium	mEq/L	≤ 125	≥ 155
Potassium	mEq/L	≤ 3.0	≥ 5.5
Calcium	mg/dL	Corrected value ≤ 7.0	Corrected value ≥ 12.0
Lactate Dehydrogenase (LDH)	U/L	No lower limit	≥ 3X ULN
Alkaline Phosphatase	U/L	No lower limit	≥ 3X ULN
Total Cholesterol	mg/dL	No lower limit	≥ 301
Uric Acid (Male)	mg/dL	No lower limit	≥ 10.5
Uric Acid (Female)	mg/dL	No lower limit	≥ 8.5
Albumin	g/dL	≤ 2.6	≥ 6.0
Total Protein	g/dL	≤ 5.0	≥ 10.0
Chloride	mEq/L	≤ 85	≥ 120
Glucose	mg/dL	≤ 45.1	≥ 200.0
Carbon Dioxide	mmol/L	≤ 9	> 40
Serum Creatinine	mg/dl	NA	> 1.5 ULN
Phosphorus	mg/dl	≤ 1.4	> 12
Magnesium	mg/dl	< 0.9	> 3
Triglycerides	mg/dl	NA	> 300
Gamma-Glutamyl Transferase [GGT]	U/L	NA	≥ 3 ULN

5.7.6 ECG

ECG parameters, general findings, heart rate, QRS complex, PR Interval, QTc interval (including corrections due to Bazett and Fridericia) are collected at Screening, Baseline, and Visits 2 through 7. Data will be summarized by treatment group at each time and changes from Baseline calculated and displayed where appropriate. The number and percentage of patients meeting the criteria for PR Interval and QTcF as defined in Table 7 below will be tabulated. These summaries will be done on both the machine-read/cardiologist readings and the semi-automated readings. For the machine-read/cardiologist data, the cardiologist reading will override the machine-read reading when they are different.

The machine read/cardiologist values are based on an automated algorithm to calculate the value and may be inaccurate due to poor quality of the ECG or abnormal waveform variations. The machine-read/cardiologist values were used for the immediate safety status of the subject.

In the semi-automated process, an iCardiac ECG analyst reviews each ECG for a more precise measurement. The iCardiac software (COMPAS) is used to determine the ECG interval measurements (QT, RR, PR, QRS). The ECG Analyst chooses 3 consecutive beats and verifies that the measurements are correct for each ECG interval or changes the measurement as appropriate. If the analyst cannot find 3 consecutive beats of good quality, a review is then done of all beats in the ECG. If there are at least 3 beats of good quality the ECG is reported. If the analyst cannot find 3 beats of good quality, then no measurement is reported for that ECG.

Table 7: ECG Criteria

ECG Parameter	Data Used in Analysis	Criteria
PR Interval (msec)	Observed[a]	> 200 msec > 220 msec > 250 msec
	Change from Baseline	≥ 30 msec to < 60 msec increases ≥ 60 msec increases Total (≥ 30 msec) increases
QTcF Interval (msec)	Observed[a]	> 450 msec > 480 msec > 500 msec

[a] A patient will be included in each criterion he or she satisfies, eg, a patient with QTc = 490 msec will be counted in the > 450 msec and > 480 msec categories.

5.7.7 Study Discontinuation due to AE/Lack of Efficacy

The number and percent of patients who discontinue from the study due to adverse event or lack of efficacy will be summarized by treatment group.

5.7.8 Extent of Exposure

Exposure to treatment will be calculated in terms of duration of treatment. Duration of treatment will be calculated as the number of days the patient has taken randomized study drug. Data will be summarized using n, mean, std, minimum, median, and maximum as described in Appendix 3 Treatment Group Rationale by Table Type.

5.7.9 Prior and Concomitant Medications

Prior medications are those taken by patients before entry into this study, and not continued while on study medication. Concomitant medications are defined as non-study medications with a start date on or before the final study visit, and that are either ongoing at the end of the study or have a stop date on or after the date of first dose of study drug. Section 5.5 of the study protocol identifies medications taken prior to study entry and the conditions under which they may be continued on a concomitant basis, as well as medications which are to be discontinued before study entry, including timing of discontinuations, and those medications prohibited to be taken during the study.

All non-study medications, including rescue medications, will be coded (WHO-Drug June 2012 Version) and tabulated by study treatment using counts and percentages.

Refer to Appendix 6 for details of imputing partial start dates of prior/concomitant medications.

5.8 Pharmacokinetic/Pharmacodynamic Analysis

Celerion, Inc. will perform pharmacokinetic parameter (C_{max} and AUC_{0-12}) estimation using plasma concentrations of DM, Dextromethorpan (DX), and Q obtained from blood samples collected on Days 36 (Visit 4) and 70 (Visit 7) of this study.

All subjects enrolled in the study will undergo a blood draw at Day 36 (Visit 4) and at Day 70 (Visit 7) for concentration analysis. Plasma concentrations of DM, DX, and quinidine (Q) will be summarized descriptively at each visit and overall and by metabolizer subgroup.

Predicted PK parameter estimations for C_{max} and AUC_{0-12} for DM, DX, and Q received from Celerion, Inc. will also be summarized descriptively, by metabolizer status. Metabolizer status will be categorized as shown in Section 5.2, Table 4 (“Normal” and “Normal or Intermediate” metabolizers will be considered “Extensive” metabolizers).

In addition, analyses exploring the association between selected PK parameters (C_{max} and AUC_{0-12}) and selected clinical outcomes (NPI Agitation/Aggression domain score, NPI4D, and NPI4A) will be performed.

6.0 GENERAL CONSIDERATIONS

6.1 Interim Analysis

There will be no interim analysis for efficacy.

Interim safety analyses will be conducted as per the DSMB charter. All necessary safeguards as described in the charter will be put into place to avoid unblinding of study staff or introduction of bias.

The DSMB tables consisted of demographics, Adverse Events, Serious Adverse Events, Physical and Neurological Examinations, Laboratory summaries by visit, Potentially Clinically Significant Laboratory Abnormalities, Treatment Compliance, Scored Assessment Inclusion Criteria, Stage 1 Randomization and NPI, ADAS-cog and MMSE by visit.

6.2 Changes from Protocol

The protocol version dated 28-Jan-2014 states in Section 8.3.4: "Additional efficacy analyses will be carried out using the ITT population." In order to enable meaningful comparisons between the results of specific exploratory analyses and the primary analysis, several exploratory analyses will be performed on the MITT population.

6.3 Pooling of Centers

There will be no consideration of study center in the formal analysis models.

6.4 Multiple Comparisons/Multiplicity

Because there is a single, pre-specified primary efficacy analysis, no corrections will be made to the Type I error.

6.5 Statistical Software Used for Analysis

All statistical analyses will be performed using SAS® version 9.1 or higher.

6.6 Treatment Group Labels

Treatment group labels used for summarization are Only Placebo, Only AVP-923, Placebo/AVP, All Placebo, and All AVP-923. See Appendix 3 for further details and rationale.

7.0 CHANGES FROM THE PREVIOUS VERSION

The following changes were made to the previous version of the Statistical Analysis Plan (August 7, 2014):

1. List of Abbreviations: Added International System of Units (SI units)
2. Section 4.2: Reference to Caregiver Distress Score was clarified. Rationale: To provide clarification around the efficacy outcome score.
3. Section 5.5.1: Addition of "Agitation" to ADCS-CGIC parameter; addition of ADCS-CGIC Overall Clinical Status parameters. Rationale: To clarify the ADCS-CGIC outcome measures and add additional analyses parameters.
4. Section 5.5.1: Addition of NPI Caregiver Distress Score outcomes to the list of secondary efficacy endpoints. Rationale: to evaluate NPI Caregiver Distress as a secondary outcome.
5. Section 5.6.2: Addition of sensitivity analysis. Rationale: To see whether removing patients who completed the NPI-NH version (rather than the standard NPI version) at all visits or at some visits has an effect on the primary results.

6. Section 5.6.3: Addition of “Agitation” to ADCS-CGIC parameter. Rationale: To clarify the outcome measure. Addition of analysis of NPI Caregiver Distress Score. Rationale: to add additional analysis parameter.

7. Section 5.6.4: Addition of two descriptive analyses. Rationale: to examine the level of “responders” in each treatment group for two different patient groupings.

8. Section 5.7.5: Added that SI units will be used for laboratory summaries. Rationale: to clarify laboratory data analysis

9. Section 5.8: Added description of metabolizer subgroups and re-mapping of reported metabolizer status. Rationale: to clarify summaries of PK data by metabolizer status.

10. Section 5.7.9: WHO-Drug version added.

11. Appendix 4: Changed “NPI Total Score” to Total NPI Score” for consistency; new analyses indicated above were added to this table for completeness.

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9.0 APPENDICES

Appendix 1: Study Schedule

			Stage 1					Stage 2		
Procedure	**Visit:**	**Screening**	**Baseline**	**Visit 2[1]**	**Visit 3[2]**	**Visit 4[2]**	**Visit 5[1]**	**Visit 6[2]**	**Visit 7[2] /ET[3]**
	Study Day:	**Day -28 to -1**	**Day 1**	**Day 8**	**Day 22**	**Day 36**	**Day 43**	**Day 57**	**Day 70**
	Study Week:	**Week -4 to -1**	**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 7**	**Week 9**	**Week 10**
Informed consent forms signed		X							
Medical history		X							
Review of inclusion and exclusion criteria		X	X						
Randomization (Stage 1)			X						
Re-Randomization (Stage 2)							X		
Physical and neurological examination		X				X			X
Record vital signs		X	X	X	X	X		X	X	X
Clinical Global Impression of Severity of Illness (CGI-S)		X	X			X		X		X
Resting 12-lead ECG		X	X	X	X	X	X	X	X	X
Review of adverse events			X	X	X	X		X	X	X
Review previous and concomitant medication		X	X	X	X	X		X	X	X
Mini-Mental State Examination (MMSE)		X				X				X
Neuropsychiatric Inventory (NPI)			X	X	X	X		X	X	X
Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog)			X			X				X
The Cornell Scale for Depression in Dementia (CSDD)		X				X				X
Activities of Daily Living Inventory (ADCS-ADL)			X			X				X
Caregiver Strain Index (CSI)			X	X	X	X		X	X	X
Patient Global Impression of Change (PGI-C) rated by the caregiver						X				X
Baseline ADCS-CGIC Evaluation			X							
Clinical Global Impression of Change (ADCS-CGIC)						X				X
Quality of Life-AD (QoL-AD)			X			X				X
Administer first dose of study medication in clinic			X				X			
Administer last dose of study medication in clinic										X
Chemistry, hematology, and urinalysis		X					X			X
Urine dipstick for females of childbearing potential only			X				X			X
Blood sample for PK assay							X			X
Blood sample for CYP2D6 genotyping			X							
Dispense study medication			X	X	X		X	X	X	
Review and return unused study medication and diary				X	X	X		X	X	X

[1] Visit 2 and Visit 5 have a + 3 days window
[2] All study visits have a ± 3 days window (except Visit 2 and Visit 5)
[3] Early Termination visit for patients who withdraw prior to study completion

Appendix 2: Algorithms for Study Instruments

Following is a table summarizing different study instruments. Exceptions to the stated rules will be noted and their impact on outcome detailed.

Individual item values and overall scores are based on the Case Report Form entries.

Instrument Name	Computational Algorithm(s), if any	Exception/Note(s)
Clinical Global Impression of Severity (CGIS)	Single number with value 1-7	A score of 0 means the instrument was not completed. Do NOT use values of 0 in any calculation.
PGIC (Patient Global Impression of Change)	Single number with value 1-7	A score of 0 means the instrument was not completed. Do NOT use values of 0 in any calculation.
Clinical Global Impression of Change (CGIC)	Single number with value 1-7	Selections are phrases which correspond exactly with numbered outcomes in PGIC.
Caregiver Strain Index (CSI)	Sum of "YES" responses ("YES" has value = 1). Range of outcomes is 0–13	If any response is missing, then total is sum of remaining responses.
Quality of Life AD (QoL-AD)	Two parts, one for Patient, the other for Caregiver. In each part the final score is the sum of individual item scores. Each item can range in value from 1 to 4 yielding maximum total scores of 52.	If "Patient not done" is checked, there should be no Patient QoL-AD score. Similarly for Caregiver if "Caregiver not done" is checked. It is possible that an individual item is not scored. The sum will then be of non-missing items only.
Mini-Mental State Examination (MMSE)	Sum of scores of 11 items, with individual items scored 0, 1, 2, 3, or 5. Maximum possible sum is 30, and minimum sum is 0 if the patient cannot successfully respond to any item.	The sum of scores can be missing if no items scored. Otherwise the sum must be ≥ 0.
Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (ADCS-ADL)	Sum of scores of 19 items. Item Scores can be 0, 1, 2, 4, or 5. Range of sum is 0 to 54.	A score of 0 can have different interpretations. For items 7 through 15, there are two possible meanings: "No" or "Don't Know." A score of 0 is valid to use in calculations. Missing individual items will be assigned a value of 0. If more than 4 of the 19 items have missing outcomes, then the sum of scores is set to missing and not used.

Instrument Name	Computational Algorithm(s), if any	Exception/Note(s)
Cornell Scale for Depression in Dementia	Sum of scores from 19 items, each item can have a value of 0, 1, or 2. Range of possible sum scores is 0-38.	An item scored as “a” or “A” is not to be included in the sum. “a” or “A” means “unable to evaluate” and is to be interpreted as a missing value. The sum is computed using non-missing scores.
Alzheimer’s Disease Assessment Scale - Cognitive Subscale (ADAS-cog)	Sum of scores from 10 items. Items have different individual scoring strategies. The first item, Word Recall Task, is scored as the mean number of incorrect responses from 3 trials of 10 words each. The mean MUST appear to 2 decimal places, ie, 7.17 and **not** 7.2. Potential total scores can range from 0 to 70.	Missing items are replaced by the "worst" score for that item. For item 1 the "worst" score is 10; items 2-5 and 8-10 the "Worst" score is 5; item 6 then "Worst" score is 8; item 7 the "Worst" score is 12.
Neuropsychiatric Inventory (NPI)	Twelve domains, either from NPI or NPI-NH (Nursing Home Version). Domain scores are the product of frequency (scored as 1 to 4) and severity (scored as 1, 2, or 3). The domain scores are summed for the total score. In this study the total score will include all 12 domains.	Each domain permits the option of checking “N/A” for Not Applicable; this is to be regarded as a missing value. There is also an option for a score of 0, meaning “Absent.” If either NA or 0 appears for a domain, there can be no non-missing frequency and severity scores, their product, or “Occupational Distress/Disruption.” A domain checked as 0 is a valid domain score and is used in calculations. The first 10 domains (A-J) are required for all patients and total scores come from them. Domains K and L are optional, and their scores are kept separate from required domains.

Appendix 3: Treatment Group Rationale by Table Type

The following table provides a general summary of table and analysis contents by broad data groupings, including appropriate stage and randomized treatments at that stage with reasoning for that display. Previous sections of this document provide greater detail on populations eligible for analysis and formal statistical methodologies to be employed.

Table Type	Rx Groups Displayed and Definition of Rx Groups		Rationale
Demographics and Baseline Characteristics (and other data assessed at Screening or Baseline)	Stage 1 Placebo	Patients randomized to Placebo at Stage 1	These summaries display data collected once, at the start of the study. Therefore the groups displayed will be the groups that patients were originally randomized to in Stage 1.
	Stage 1 AVP-923	Patients randomized to AVP-923 at Stage 1	
Demographics and Baseline Characteristics (and other data assessed at Screening or Baseline)	Stage 2 Placebo	Patients re-randomized to placebo at Stage 2	These summaries display data collected once, at the start of the study. The groups displayed will be the groups that patients were re-randomized to in Stage 2.
	Stage 2 AVP-923	Patients re-randomized to AVP-923 in Stage 2	
NPI change from Baseline (and all other efficacy summaries)	Placebo	Patients randomized to Placebo at Stage 1 who were responders at Stage 1 and Placebo non-responders from Stage 1 who were re-randomized to Placebo at Stage 2	Per the SPCD design
	AVP-923	Patients randomized to AVP-923 at Stage 1 and Placebo non-responders from Stage 1 who were re-randomized to AVP-923 at Stage 2	

Table Type	Rx Groups Displayed and Definition of Rx Groups		Rationale
AE and PCS Lab summaries	Only Placebo	Patients who only received Placebo	Summarizes all AEs that occurred in the study under the drug taken at the time. Note that Patients in the Placebo/AVP group will be counted in both the All Placebo and All AVP-923 columns. Similar rationale as the AE summaries, the PCS summaries includes all incidences of PCS criteria that occurred in the study under the drug taken at the time. Note that Patients in the Placebo/AVP group will be counted in both the All Placebo and All AVP-923 columns.
	Only AVP-923	Patients who only received AVP-923	
	Placebo/AVP-923: Placebo	For Patients in the Placebo/AVP-923 group, AEs that occurred while on Placebo	
	Placebo/AVP-923: AVP-923	For Patients in the Placebo/AVP group, AEs that occurred while on AVP-923	
	All Placebo	Patients who took Placebo at either stage – All AEs that occurred on Placebo	
	All AVP-923	Patients who took AVP-923 at either stage – All AEs that occurred while on AVP-923	
Patient Disposition	Only Placebo	Patients who only received Placebo	Similar to AE groupings. However, while AEs can occur in both stages of the study, a patient can only discontinue from the study once. Therefore all withdrawals or completions in the Placebo/AVP-923 group will occur while on AVP-923. An All Placebo column is not needed since it would be the same as the 'only' Placebo column. The first 3 columns will add up to the Overall column.
	Only AVP-923	Patients who only received AVP-923	
	Placebo/AVP-923	Patients re-randomized to AVP-923 in Stage 2	
	All AVP-923	All patients who received AVP-923 during the study. This will be a sum of the AVP-923 and Placebo/AVP columns.	
	Overall	All Patients	
Patient Status	Stage 1 AVP-923	Randomized group in Stage 1	Provides a summary of patient flow in the study, similar to a cohort diagram. May not need the Stage 1 and Stage 2 identifiers because apparent from the table.
	Stage 1 Placebo	Randomized group in Stage 1	
	Stage 2 Placebo (subgroup under Placebo column)	Randomized group in Stage 2	
	Stage 2 AVP-923 (subgroup under Placebo column)	Randomized group in Stage 2	
Change from Baseline, Physical and Neurological Examination Summaries	Only Placebo	Patients who only received Placebo	Stage 1 study medication will represent Baseline for both the Only Placebo and Only AVP-923 treatment groups. As these patients remained on the same medication
	Only AVP-923	Patients who only received AVP-923	
	Placebo/AVP-923	Patients re-randomized to AVP-923 in Stage 2	

Table Type	Rx Groups Displayed and Definition of Rx Groups		Rationale
Lab Shift Tables			throughout the study, the original Stage 1 Baseline assessment is used to compare all post-Baseline assessments. For the Placebo/AVP-923 treatment group, Baseline is the last assessment prior to receiving study medication in a given stage. Since patients receive both Placebo and AVP-923, Baseline changes will depend on last assessment prior to stage randomization.
	Only Placebo	Patients who only received Placebo	Baseline will be defined as the last assessment prior to receiving study medication. For Patients receiving Placebo during Stage 1 and re-randomized to AVP-923 at Stage 2, Baseline will be defined as last assessment prior to re-randomization and summarized as AVP-923.
	AVP-923	Patients randomized to either AVP-923 at either stage.	

Appendix 4: Efficacy Analyses

Efficacy Endpoint	Comparison	Data Grouping (Figure 1)	Population	Treatment Groups Displayed on Table	Statistical Method	Interpretation	SAP Section
NPI Agitation/Aggression Domain	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Primary analysis	5.4.1 – 5.4.2
NPI Agitation/Aggression Domain	Change from Stage 2 Baseline to Visits 5 and 6	C x D	MITT	Placebo, AVP-923	ANCOVA	Secondary	5.5.1
NPI Agitation/Aggression Domain	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	Week 4 Evaluable	Placebo, AVP-923	SPCD	Exploratory	5.6.3
NPI Agitation/Aggression Domain	Change from Stage 1 Baseline to Visits 2 and 3, and change from Stage 2 Baseline to Visits 5 and 6	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Secondary/ evaluation of 20/10 effect	5.5.1
NPI Agitation/Aggression Domain	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Exploratory /alternative definition of Responder	5.6.3
NPI Agitation/Aggression Domain	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and (C + E x D + F)	MITT	Placebo, AVP-923	SPCD	Exploratory/ including Placebo Responders	5.6.4
NPI Agitation/Aggression Domain	Change from Stage 2 Baseline to Visits 5 and 6	C x D	MITT	Placebo, AVP-923	ANCOVA	Exploratory/ alternative definition of Responder	5.6.3
NPI Agitation/Aggression Domain	Change from Stage 2 Baseline to Visits 5 and 6	(C + E) x (D + F)	MITT	Placebo, AVP-923	ANCOVA	Exploratory/ including Placebo responders	5.6.4
NPI Agitation/Aggression Domain	Change from Stage 1 Baseline to Visits 2 and 3, and Stage 2 Baseline to Visits 5 and 6	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Exploratory/ alternative definition of Responder	5.6.3
NPI Agitation/Aggression Domain	Change from Stage 1 Baseline to Visits 2 and 3, and Stage 2 Baseline to Visits 5 and 6	A x B and (C + E x D + F)	MITT	Placebo, AVP-923	SPCD	Exploratory/ including Placebo responders	5.6.4
NPI Agitation/Aggression Domain	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	ITT/CitAD patient subset	Placebo, AVP-923	SPCD	Exploratory	5.6.5

Efficacy Endpoint	Comparison	Data Grouping (Figure 1)	Population	Treatment Groups Displayed on Table	Statistical Method	Interpretation	SAP Section
NPI Agitation/Aggression Domain	Change from Stage 2 Baseline to Visits 5 and 6	C x D	ITT/CitAD patient subset	Placebo, AVP-923	ANCOVA	Exploratory	5.6.5
NPI Agitation/Aggression Domain	Change from Stage 1 Baseline to Visits 2 and 3, and change from Stage 2 Baseline to Visits 5 and 6	A x B and C x D	ITT/CitAD patient subset	Placebo, AVP-923	SPCD	Exploratory	5.6.5
NPI Agitation/Aggression Domain	Change from Stage 1 Baseline to each visit	A x B and C x D	MITT	Placebo, AVP-923	Repeated measures mixed model	Exploratory Sensitivity	5.6.2
NPI Agitation/Aggression Domain	Change from Stage 1 Baseline to each visit	(A + C + E) x (B + D + F + G)	ITT	Placebo, AVP-923	Repeated measures mixed model	Exploratory Sensitivity	5.6.2
NPI Agitation/Aggression Domain	Actual scores at each visit	(A + C + E) x (B + G)	ITT	Only Placebo, Only AVP-923	Longitudinal analysis/linear mixed effects model	Exploratory	5.6.4
NPI Agitation/Aggression	Change from Baseline to Visit 7/LOCF	(A + C + E) x (B + G)	ITT	Only Placebo, Only AVP-923	ANCOVA	Exploratory	5.6.4
NPI Agitation/Aggression	Change from Stage 1 Baseline to Visit 4	A x B	MITT	Placebo, AVP-923	ANCOVA	Exploratory	5.6.4
NPI Agitation/Aggression	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT, CGI-S =4 vs. >4 at Stage 1 Baseline	Placebo, AVP-923	Descriptive	Exploratory	5.6.5
NPI Agitation/Aggression	Percent Decrease at Visit 4 from Stage 1 Baseline >=25%, >=50%, >=75%	(A + C + E) x (B + G)	MITT	Placebo, AVP-923	Descriptive	Exploratory	5.6.4
NPI Agitation/Aggression	Percent Decrease at Visit 7 from Stage 2 Baseline >=25%, >=50%, >=75%	(C + E) x (D + F)	MITT	Placebo, AVP-923	Descriptive	Exploratory	5.6.4
NPI Agitation/Aggression Domain	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT, excluding patients using different versions of NPI	Placebo, AVP-923	SPCD	Exploratory Sensitivity analysis	5.6.2

Efficacy Endpoint	Comparison	Data Grouping (Figure 1)	Population	Treatment Groups Displayed on Table	Statistical Method	Interpretation	SAP Section
NPI Agitation/Aggression Domain	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT, excluding patients using NPI-NH throughout	Placebo, AVP-923	SPCD	Exploratory Sensitivity analysis	5.6.2
NPI4D	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Secondary	5.5.1
NPI4D	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Exploratory/alternative definition of Responder	5.6.3
NPI4D	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and (C + E x D + F)	MITT	Placebo, AVP-923	SPCD	Exploratory/including Placebo responders	5.6.4
NPI4D	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	ITT/CitAD patient subset	Placebo, AVP-923	SPCD	Exploratory	5.6.5
NPI4D	Actual scores at each visit	(A + C + E) x (B + G)	ITT	Only Placebo, Only AVP-923	Longitudinal analysis/linear mixed effects model	Exploratory	5.6.4
NPI4D	Change from Baseline to Visit 7/LOCF	(A + C + E) x (B + G)	ITT	Only Placebo, Only AVP-923	ANCOVA	Exploratory	5.6.4
NPI 4D	Change from Stage 1 Baseline to Visit 4	A x B	MITT	Placebo, AVP-923	ANCOVA	Exploratory	5.6.4
NPI4D	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT, CGI-S =4 vs. >4 at Stage 1 Baseline	Placebo, AVP-923	Descriptive	Exploratory	5.6.5
NPI4D	Percent Decrease at Visit 4 from Stage 1 Baseline >=25%, >=50%, >=75%	(A + C + E) x (B + G)	MITT	Placebo, AVP-923	Descriptive	Exploratory	5.6.4
NPI4D	Percent Decrease at Visit 7 from Stage 2 Baseline >=25%, >=50%, >=75%	(C + E) x (D + F)	MITT	Placebo, AVP-923	Descriptive	Exploratory	5.6.4

Efficacy Endpoint	Comparison	Data Grouping (Figure 1)	Population	Treatment Groups Displayed on Table	Statistical Method	Interpretation	SAP Section
NPI4D	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT, excluding patients using different versions of NPI	Placebo, AVP-923	SPCD	Exploratory Sensitivity analysis	5.6.2
NPI4D	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT, excluding patients using NPI-NH throughout	Placebo, AVP-923	SPCD	Exploratory Sensitivity analysis	5.6.2
NPI4A	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Secondary	5.5.1
NPI4A	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Exploratory/alternative definition of Responder	5.6.3
NPI4A	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and (C + E x D + F)	MITT	Placebo, AVP-923	SPCD	Exploratory/including Placebo responders	5.6.4
NPI4A	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	ITT/CitAD patient subset	Placebo, AVP-923	SPCD	Exploratory	5.6.5
NPI4A	Actual scores at each visit	(A + C + E) x (B + G)	ITT	Only Placebo, Only AVP-923	Longitudinal Analysis/linear mixed effects model	Exploratory	5.6.4
NPI4A	Change from Baseline to Visit 7/LOCF	(A + C + E) x (B + G)	ITT	Only Placebo, Only AVP-923	ANCOVA	Exploratory	5.6.4
NPI4A	Change from Stage 1 Baseline to Visit 4	A x B	MITT	Placebo, AVP-923	ANCOVA	Exploratory	5.6.4
NPI4A	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT, CGI-S =4 vs. >4 at Stage 1 Baseline	Placebo, AVP-923	Descriptive	Exploratory	5.6.5
NPI4A	Percent Decrease at Visit 4 from Stage 1 Baseline >=25%, >=50%, >=75%	(A + C + E) x (B + G)	MITT	Placebo, AVP-923	Descriptive	Exploratory	5.6.4

Efficacy Endpoint	Comparison	Data Grouping (Figure 1)	Population	Treatment Groups Displayed on Table	Statistical Method	Interpretation	SAP Section
NPI4A	Percent Decrease at Visit 7 from Stage 2 Baseline >=25%, >=50%, >=75%	(C + E) x (D + F)	MITT	Placebo, AVP-923	Descriptive	Exploratory	5.6.4
NPI4A	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT, excluding patients using different versions of NPI	Placebo, AVP-923	SPCD	Exploratory Sensitivity analysis	5.6.2
NPI4A	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT, excluding patients using NPI-NH throughout	Placebo, AVP-923	SPCD	Exploratory Sensitivity analysis	5.6.2
Total NPI Score	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Secondary	5.5.1
Total NPI Score	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Exploratory/alternative definition of Responder	5.6.3
Total NPI Score	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and (C + E x D + F)	MITT	Placebo, AVP-923	SPCD	Exploratory/including Placebo responders	5.6.4
Total NPI Score	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	ITT/CitAD patient subset	Placebo, AVP-923	SPCD	Exploratory	5.6.5
Total NPI Score	Actual scores at each visit	(A + C + E) x (B + G)	ITT	Only Placebo, Only AVP-923	Longitudinal Analysis/linear mixed effects model	Exploratory	5.6.4
Total NPI Score	Change from Baseline to Visit 7/LOCF	(A + C + E) x (B + G)	ITT	Only Placebo, Only AVP-923	ANCOVA	Exploratory	5.6.4
Total NPI Score	Percent Decrease at Visit 4 from Stage 1 Baseline >=25%, >=50%, >=75%	(A + C + E) x (B + G)	MITT	Placebo, AVP-923	Descriptive	Exploratory	5.6.4
Total NPI Score	Percent Decrease at Visit 7 from Stage 2 Baseline >=25%, >=50%, >=75%	(C + E) x (D + F)	MITT	Placebo, AVP-923	Descriptive	Exploratory	5.6.4

Efficacy Endpoint	Comparison	Data Grouping (Figure 1)	Population	Treatment Groups Displayed on Table	Statistical Method	Interpretation	SAP Section
Total NPI Score	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT, excluding patients using different versions of NPI	Placebo, AVP-923	SPCD	Sensitivity analysis	5.6.2
Total NPI Score	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT, excluding patients using NPI-NH throughout	Placebo, AVP-923	SPCD	Sensitivity analysis	5.6.2
All Other NPI Domains separately	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Secondary	5.5.1
All Other NPI Domains separately	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Exploratory/alternative definition of Responder	5.6.3
All Other NPI Domains separately	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and (C + E x D + F)	MITT	Placebo, AVP-923	SPCD	Exploratory/including Placebo responders	5.6.4
All Other NPI Domains separately	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	ITT/CitAD patient subset	Placebo, AVP-923	SPCD	Exploratory	5.6.5
All Other NPI Domains separately	Actual scores at each visit	(A + C + E) x (B + G)	ITT	Only Placebo, Only AVP-923	Longitudinal Analysis/linear mixed effects model	Exploratory	5.6.4
All Other NPI Domains separately	Change from Baseline to Visit 7/LOCF	(A + C + E) x (B + G)	ITT	Only Placebo, Only AVP-923	ANCOVA	Exploratory	5.6.4
NPI Caregiver Distress Score for NPI Agitation/Aggression Domain	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Secondary	5.6.3
NPI Caregiver Distress Score for NPI Agitation/Aggression Domain	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Exploratory/alternative definition of Responder	5.6.3
NPI Caregiver Distress Score for NPI Agitation/Aggression Domain	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and (C + E x D + F)	MITT	Placebo, AVP-923	SPCD	Exploratory/including Placebo responders	5.6.4

Efficacy Endpoint	Comparison	Data Grouping (Figure 1)	Population	Treatment Groups Displayed on Table	Statistical Method	Interpretation	SAP Section
NPI Caregiver Distress Score for NPI Agitation/Aggression Domain	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	ITT/CitAD patient subset	Placebo, AVP-923	SPCD	Exploratory	5.6.5
NPI Caregiver Distress Score for Total NPI	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Secondary	5.6.3
NPI Caregiver Distress Score for Total NPI	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Exploratory/alternative definition of Responder	5.6.3
NPI Caregiver Distress Score for Total NPI	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and (C + E x D + F)	MITT	Placebo, AVP-923	SPCD	Exploratory/including Placebo responders	5.6.4
NPI Caregiver Distress Score for Total NPI	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	ITT/CitAD patient subset	Placebo, AVP-923	SPCD	Exploratory	5.6.5
NPI Caregiver Distress Score for NPI4D	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Secondary	5.6.3
NPI Caregiver Distress Score for NPI4D	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Exploratory/alternative definition of Responder	5.6.3
NPI Caregiver Distress Score for NPI4D	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and (C + E x D + F)	MITT	Placebo, AVP-923	SPCD	Exploratory/including Placebo responders	5.6.4
NPI Caregiver Distress Score for NPI4D	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	ITT/CitAD patient subset	Placebo, AVP-923	SPCD	Exploratory	5.6.5
NPI Caregiver Distress Score for NPI4A	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Secondary	5.6.3
NPI Caregiver Distress Score for NPI4A	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Exploratory/alternative definition of Responder	5.6.3
NPI Caregiver Distress Score for NPI4A	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and (C + E x D + F)	MITT	Placebo, AVP-923	SPCD	Exploratory/including Placebo responders	5.6.4
NPI Caregiver Distress Score for NPI4A	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	ITT/CitAD patient subset	Placebo, AVP-923	SPCD	Exploratory	5.6.5

Efficacy Endpoint	Comparison	Data Grouping (Figure 1)	Population	Treatment Groups Displayed on Table	Statistical Method	Interpretation	SAP Section
CSI	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Secondary	5.5.1
CSI	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Exploratory/alternative definition of Responder	5.6.3
CSI	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and (C + E x D + F)	MITT	Placebo, AVP-923	SPCD	Exploratory/including Placebo responders	5.6.4
CSI	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	ITT/CitAD patient subset	Placebo, AVP-923	SPCD	Exploratory	5.6.5
CSI	Actual scores at each visit	(A + C + E) x (B + G)	ITT	Only Placebo, Only AVP-923	Longitudinal Analysis/linear mixed effects model	Exploratory	5.6.4
CSI	Change from Baseline to Visit 7/LOCF	(A + C + E) x (B + G)	ITT	Only Placebo, Only AVP-923	ANCOVA	Exploratory	5.6.4
ADCS-ADL	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Secondary	5.5.1
ADCS-ADL	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Exploratory/alternative definition of Responder	5.6.3
ADCS-ADL	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and (C + E x D + F)	MITT	Placebo, AVP-923	SPCD	Exploratory/including Placebo responders	5.6.4
ADCS-ADL	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	ITT/CitAD patient subset	Placebo, AVP-923	SPCD	Exploratory	5.6.5
ADCS-ADL	Change from Baseline to Visit 7/LOCF	(A + C + E) x (B + G)	ITT	Only Placebo, Only AVP-923	ANCOVA	Exploratory	5.6.4
QoL-AD	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Secondary	5.5.1
QoL-AD	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Exploratory/alternative definition of Responder	5.6.3

Efficacy Endpoint	Comparison	Data Grouping (Figure 1)	Population	Treatment Groups Displayed on Table	Statistical Method	Interpretation	SAP Section
QoL-AD	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and (C + E x D + F)	MITT	Placebo, AVP-923	SPCD	Exploratory/including Placebo responders	5.6.4
QoL-AD	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	ITT/CitAD patient subset	Placebo, AVP-923	SPCD	Exploratory	5.6.5
QoL-AD	Change from Baseline to Visit 7/LOCF	(A + C + E) x (B + G)	ITT	Only Placebo, Only AVP-923	ANCOVA	Exploratory	5.6.4
CSDD	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Secondary	5.5.1
CSDD	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Exploratory/alternative definition of Responder	5.6.3
CSDD	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and (C + E x D + F)	MITT	Placebo, AVP-923	SPCD	Exploratory/including Placebo responders	5.6.4
CSDD	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	ITT/CitAD patient subset	Placebo, AVP-923	SPCD	Exploratory	5.6.5
CSDD	Change from Baseline to Visit 7/LOCF	(A + C + E) x (B + G)	ITT	Only Placebo, Only AVP-923	ANCOVA	Exploratory	5.6.4
MMSE	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Secondary	5.5.1
MMSE	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Exploratory/alternative definition of Responder	5.6.3
MMSE	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and (C + E x D + F)	MITT	Placebo, AVP-923	SPCD	Exploratory/including Placebo responders	5.6.4
MMSE	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	ITT/CitAD patient subset	Placebo, AVP-923	SPCD	Exploratory	5.6.5
MMSE	Change from Baseline to Visit 7/LOCF	(A + C + E) x (B + G)	ITT	Only Placebo, Only AVP-923	ANCOVA	Exploratory	5.6.4
ADCS-CGIC Agitation	Summary of Scores at Visit 4 and Visit 7 (Relative to Stage 1 Baseline)	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Secondary	5.5.1

Efficacy Endpoint	Comparison	Data Grouping (Figure 1)	Population	Treatment Groups Displayed on Table	Statistical Method	Interpretation	SAP Section
ADCS-CGIC Agitation	Summary of Scores at Visit 4 and Visit 7(Relative to Stage 1 Baseline)	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Exploratory/alternative definition of Responder	5.6.3
ADCS-CGIC Agitation	Summary of Scores at Visit 4 and Visit 7(Relative to Stage 1 Baseline)	A x B and (C + E x D + F)	MITT	Placebo, AVP-923	SPCD	Exploratory/including Placebo responders	5.6.4
ADCS-CGIC Agitation	Summary of Scores at Visit 4 and Visit 7(Relative to Stage 1 Baseline)	A x B and C x D	ITT/CitAD patient subset	Placebo, AVP-923	SPCD	Exploratory	5.6.5
ADCS-CGIC Agitation	Summary of Scores at Visit 4 and Visit 7(Relative to Stage 1 Baseline)	A x B and C x D	Week 4 Evaluable	Placebo, AVP-923	SPCD	Exploratory	5.6.3
ADCS-CGIC Agitation	Summary of Scores at Visit 4 and Visit 7(Relative to Visit 4)	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Secondary	5.5.1
ADCS-CGIC Agitation	Summary of Scores at Visit 4 and Visit 7(Relative to Visit 4)	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Exploratory/alternative definition of Responder	5.6.3
ADCS-CGIC Agitation	Summary of Scores at Visit 4 and Visit 7(Relative to Visit 4)	A x B and (C + E x D + F)	MITT	Placebo, AVP-923	SPCD	Exploratory/including Placebo responders	5.6.4
ADCS-CGIC Agitation	Summary of Scores at Visit 4 and Visit 7(Relative to Visit 4)	A x B and C x D	ITT/CitAD patient subset	Placebo, AVP-923	SPCD	Exploratory	5.6.5
ADCS-CGIC Agitation	Summary of Scores at Visit 4 and Visit 7(Relative to Visit 4)	A x B and C x D	Week 4 Evaluable	Placebo, AVP-923	SPCD	Exploratory	5.6.3
ADCS-CGIC Agitation	Summary of Scores at Visit 4 and Visit 7	A x B and C x D	MITT	Placebo, AVP-923	Proportional Odds Regression	Exploratory	5.6.3
PGI-C	Summary of Scores at Visit 4 and Visit 7 (Relative to Baseline)	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Secondary	5.5.1
ADCS-CGIC Overall Clinical Status	Summary of Scores at Visit 4 and Visit 7 (Relative to Stage 1 Baseline)	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Secondary	5.5.1
ADCS-CGIC Overall Clinical Status	Summary of Scores at Visit 4 and Visit 7(Relative to Visit 4)	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Secondary	5.5.1

Efficacy Endpoint	Comparison	Data Grouping (Figure 1)	Population	Treatment Groups Displayed on Table	Statistical Method	Interpretation	SAP Section
PGI-C	Summary of Scores at Visit 4 and Visit 7(Relative to Baseline)	A x B and C x D	MITT	Placebo, AVP-923	SPCD	Exploratory/alternative definition of Responder	5.6.3
PGI-C	Summary of Scores at Visit 4 and Visit 7(Relative to Baseline)	A x B and (C + E x D + F)	MITT	Placebo, AVP-923	SPCD	Exploratory/including Placebo responders	5.6.4
PGI-C	Summary of Scores at Visit 4 and Visit 7(Relative to Baseline)	A x B and C x D	ITT/CitAD patient subset	Placebo, AVP-923	SPCD	Exploratory	5.6.5
PGI-C	Summary of Scores at Visit 4 and Visit 7	A x B and C x D	MITT	Placebo, AVP-923	Proportional Odds Regression	Exploratory	5.6.3
ADAS-Cog	Change from Stage 1 Baseline to Visit 4 and Stage 2 Baseline to Visit 7	A x B and C x D	ITT	Placebo, AVP-923	SPCD	Exploratory	5.6.1
Changes in Allowed Psychotropic Medications		(A + C + E), (B + G), (A + D + F), (B + D + F + G)	MITT	Only Placebo, Only AVP-923, Placebo/AVP-923, All AVP-923, Overall	Descriptive	Secondary	5.5.2
Rescue Medication (Oral Lorazepam) Use		(A + C + E) x (B + G)	MITT	Only Placebo, Only AVP-923, Placebo/AVP-923, All AVP-923, Overall	Descriptive	Secondary	5.52

Appendix 5: Adverse Event Start/Stop Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Imputation
Start date for AEs	D	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month
	D and M	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y prior to Y of first dose of study drug but same as Y of screening date	Date of screening date
	D, M, Y	None - date completely missing	Date of first dose of study drug
Stop date for AEs	D	M and Y same as M and Y of last dose of study drug	Date of last dose of study drug
		M and/or Y not same as date of last dose of study drug	Use last day of month
	D and M	Y same as Y of last dose of study drug	Date of last dose of study drug
		Y not same as Y of last dose of study drug	Use Dec 31
	D, M, Y	None - date completely missing	No imputation, but assume ongoing

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month.

Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.

Appendix 6: Prior and Concomitant Medication Start Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Imputation
Start date for con meds	D only	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month
	M and D	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y not same as Y of first dose of study drug	Use Jan 01 of Y
	M, D, and Y	None - date completely missing	Day prior to date of first dose of study drug
Stop date for con meds	D only	M and Y same as M and Y of last dose of study drug	Date of last dose of study drug
		M and/or Y not same as date of last dose of study drug	Last day of month
	M and D	Y same as Y of last dose of study drug	Date of last dose of study drug
		Y not same as Y of last dose of study drug	Use Dec 31 of Y
	M, D, and Y	None - date completely missing and NOT ongoing	Date of last dose of study drug

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month.

Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.

Appendix 7: Medical History Start Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Imputation
Start date for medical history	D only	M and Y prior to screening date	Last day of month
		M and Y same as screening date	Day prior to screening date
	M and D	Y prior to year of screening date	Jan 1 of Y
		Y is same as screening year	Day prior to screening date
	M, D, and Y	None - date completely missing	Keep as missing